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- Yeast competent cells included
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Kit components sold separately

***K. lactis* GG799 Competent Cells** **C1001**

pKLAC1 Vector **N3740**

	K. lactis	*P. pastoris*
High yield expression	✓	✓
Rapid high cell density growth	✓	✓
Yeast Competent Cells Included	✓	
Methanol-free growth media	✓	
Antibiotic-free Selection	✓	
Enhanced multi-copy integration	✓	
Protein folding and glycosylation	✓	✓
Expression of genes toxic to *E. coli*	✓	✓

Quick comparison of *K. lactis* and *P. pastoris* expression systems.

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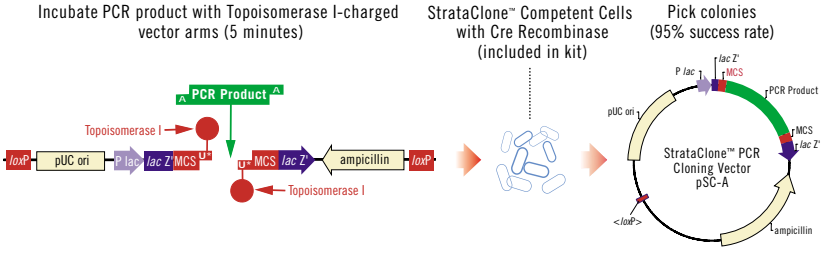

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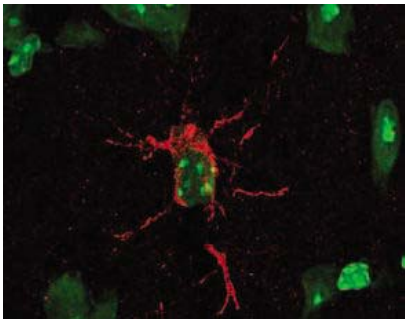
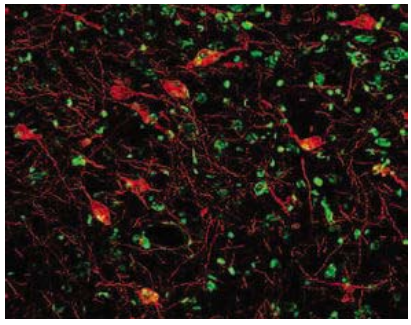


Detection of NGF Receptor in cryostat tissue sections of mouse brain using R&D Systems goat anti-mouse NGF R affinity-purified polyclonal antibody (Catalog # AF1157). Tissues were stained using Texas Red (red) and counterstained with Fluoro Nissl Green (green).



Detection of Neprilysin in cryostat tissue sections of mouse brain using R&D Systems goat anti-mouse Neprilysin affinity-purified polyclonal antibody (Catalog # AF1126).Tissues were stained using Texas Red (red) and counterstained with Fluoro Nissl Green (green).

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COVER

The "hot Jupiter" planet υ Andromedae b bakes under its nearby star in this artist's concept. NASA's Spitzer Space Telescope determined that, unlike Jupiter and Saturn, the planet redistributes little of its received heat to the night side, resulting in a dayside hot spot about 1400 K warmer than the planet's night side. See page 623.

Illustration: NASA/JPL-Caltech/Robert Hurt

DEPARTMENTS

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PERSPECTIVES

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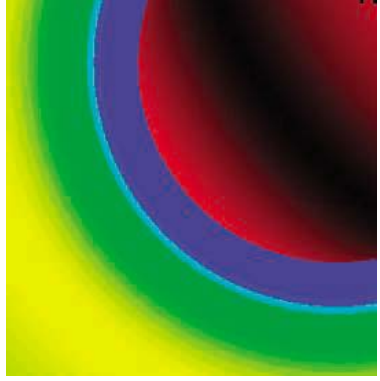
GENETICS

A Genome-Wide Association Study Identifies *IL23R* as an Inflammatory Bowel Disease Gene
R. H. Duerr et al.
People with a rare sequence variant of the gene encoding the receptor for an immunological cytokine have a reduced risk of inflammatory bowel disease.
10.1126/science.1135245

PHYSICS

Dynamical Superconducting Order Parameter Domains in Sr_2RuO_4
F. Kidwingira, J. D. Strand, D. J. Van Harlingen, Y. Maeno
Direct observations reveal that strontium ruthenate becomes superconducting through complex p-wave electron pairing, as predicted by theory.
10.1126/science.1133239

LETTER: A Plea for Justice for Jailed Medical Workers
S. K. Ahuja et al.
>> News story p. 581
10.1126/science.1136578



ASTROPHYSICS

Deep Mixing of ^3He: Reconciling Big Bang and Stellar Nucleosynthesis
P. P. Eggleton, D. S. P. Dearborn, J. C. Lattanzio
Three-dimensional models of giant stars show that deep convection of supposedly stable layers destroys ^3He to levels consistent with the Big Bang predictions.
10.1126/science.1133065

ASTRONOMY

Fast Variability of Tera–Electron Volt γ Rays from the Radio Galaxy M87
F. Aharonian et al.
Very-high-energy gamma rays from the radio galaxy M87 vary daily, implying that they originate close to a central supermassive black hole.
10.1126/science.1134408

TECHNICAL COMMENT ABSTRACTS

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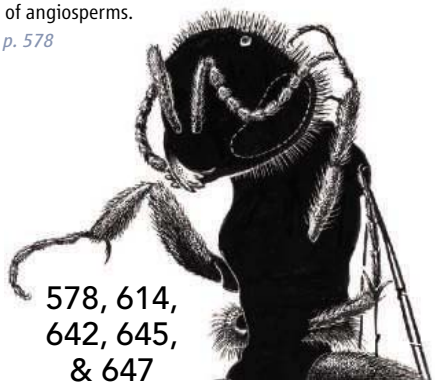

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Pierce ECL Reagent
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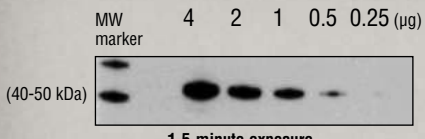

1.5-minute exposure

GE Healthcare ECL Reagent
Protein per well

1.5-minute exposure

Pierce ECL Substrate Western blot detection of Actin (Beta) from HeLa cell lysate. Dilutions of HeLa cell lysate were prepared and separated by electrophoresis. The proteins were transferred to nitrocellulose membranes (Product # 88025) and the membranes were blocked with 5% skim milk. After blocking, the membranes were incubated with Mouse Anti-Human Actin β (US Biological, Swampscott, MA) at 1 µg/ml. The membranes were washed and then incubated with 0.2 µg/ml of HRP-conjugated Goat anti-Mouse IgG (Product # 31430) and then washed again. Working solutions of the substrates were prepared according to the manufacturers' instructions and added to the membranes for 1 minute. The membranes were removed from the substrates and placed in plastic sheet protectors. Each membrane was exposed to CL-XPosure™ Film (Product # 34090) for 90 seconds.

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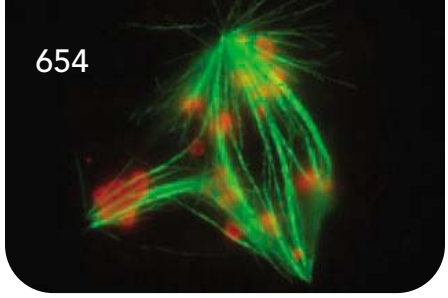

REPORTS *CONTINUED...*

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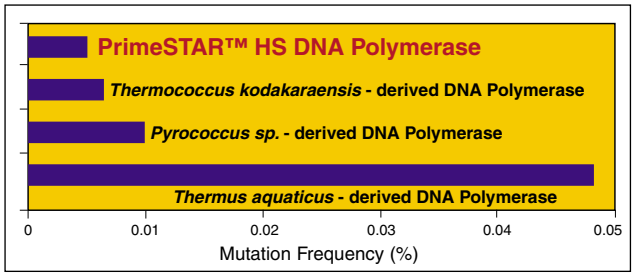
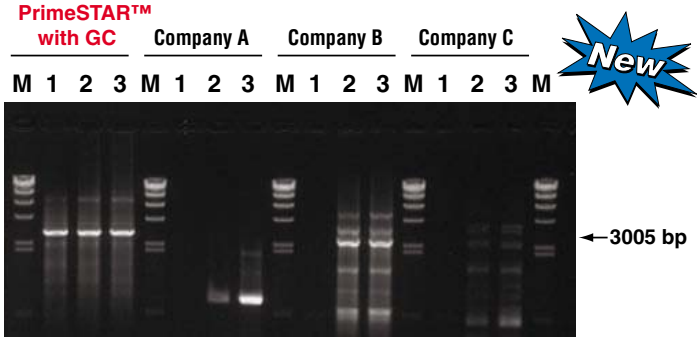


PrimeSTAR™ Fidelity Comparison with Other DNA Polymerases and *Taq*.



Amplification of a 3005 bp high-GC (73.2%) TthHB8 genomic DNA template. The performance of high fidelity, high-GC enzymes from Companies A, B, and C was compared with PrimeSTAR™ HS DNA Polymerase with GC Buffer. Lanes 1, 2, and 3: 100 pg, 1 ng, 10 ng human genomic DNA template.

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A Bumpy Road for Stem Cells
Transplanted stem cells cure Parkinson's in mice but also lead to tumors.

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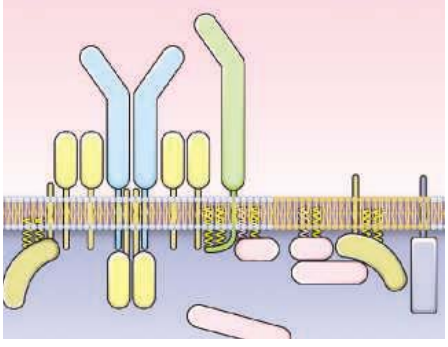
Two new studies keep hope for martian microbes alive.

Brain Zap Makes Rats a Little Smarter
Stimulating central thalamus with electrodes boosts learning in rodents.



Palmitoylation in T cell signaling.

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REVIEW: Palmitoylation of Ligands, Receptors, and Intracellular Signaling Molecules
M. D. Resh
Palmitoylation plays roles in membrane binding, targeting, and trafficking of proteins involved in cell signaling.

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Find out how to use *C. elegans* to help students bridge the gap between research and education; in Educator Sites.

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S. A. Webb
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FRANCE: Different Prospects
A. Hellemans
Graduates of French universities have fewer prospects in industrial research than Grandes Ecoles graduates have.

CANADA: Walking the Pharmacogenomic Tightrope
A. Fazekas
Alzheimer's researcher Judes Poirier maintains a fine balance between academia and industry.

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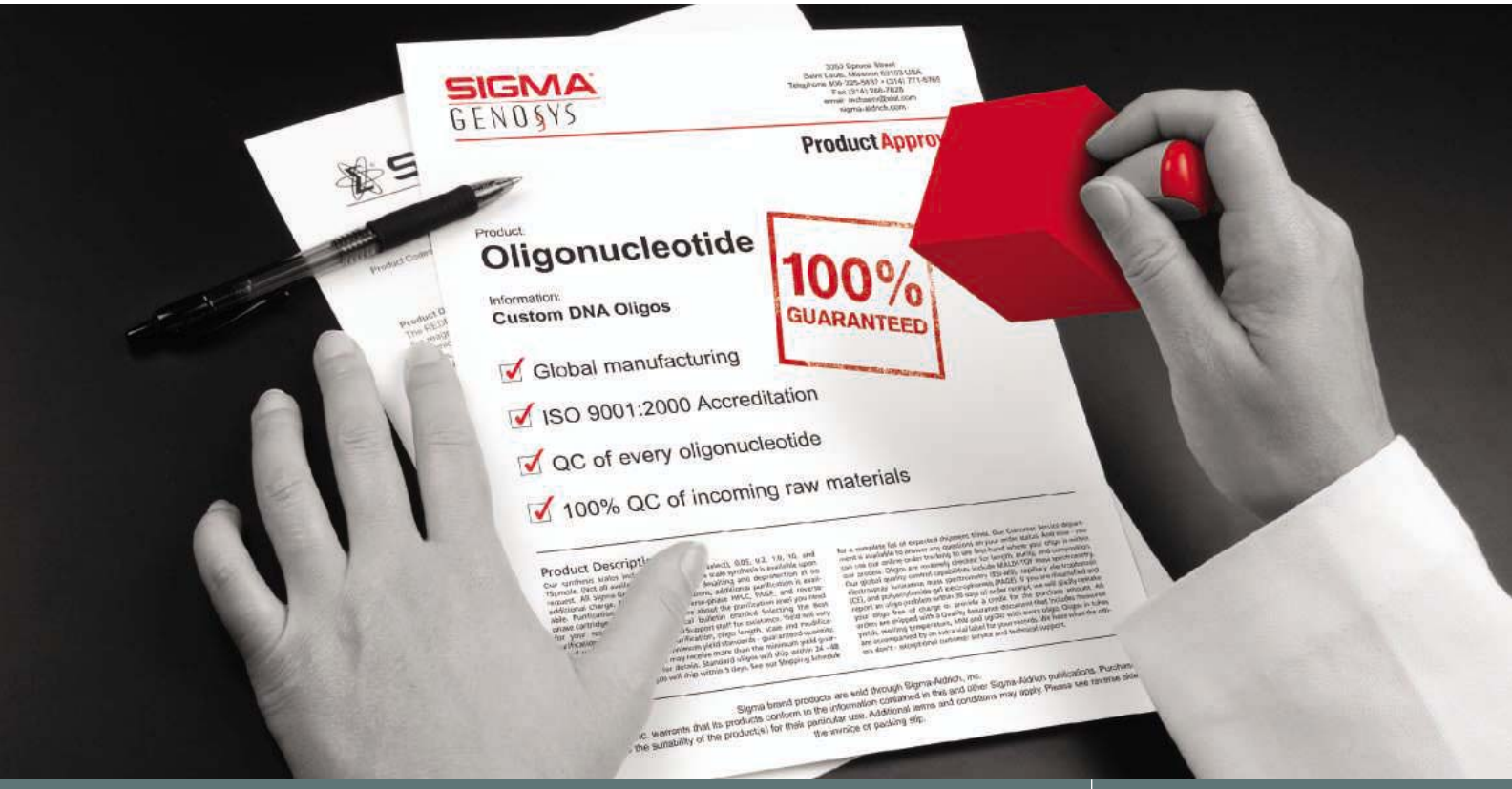

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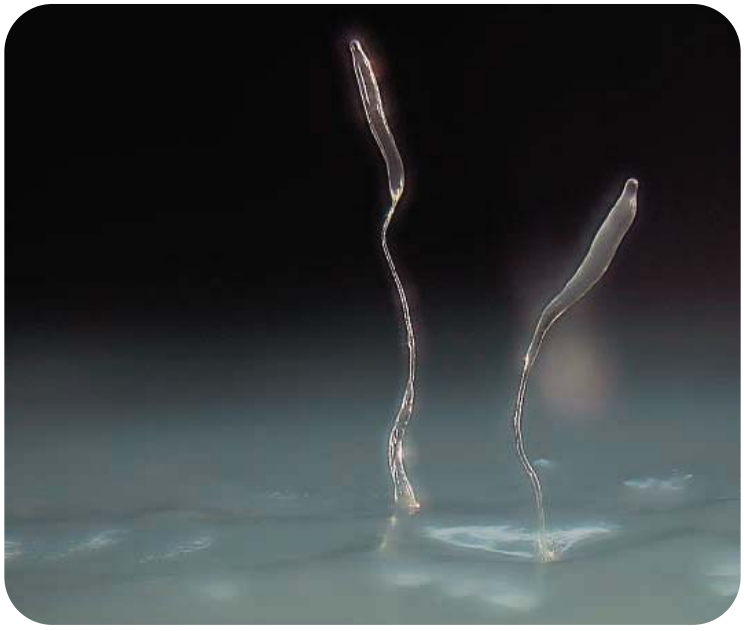


Rethinking Slime Mold Taxonomy

Despite the interest in *Dictyostelium discoideum* as a model system, little or no molecular data exist for the rest of this ancient and morphologically diverse group. Their current taxonomy, first described more than 50 years ago, is based purely on morphology. **Schaap *et al.*** (p. 661) have constructed a molecular phylogeny of the Dictyostelia based on two independent molecular markers that includes nearly every one of the more than 90 recognized species. The tree, which resolves into four major taxa, bears little resemblance to the morphologically based tree.

Who Gains Wins?

We are all aware that information technology can be compromised by spam e-mails, online fraud, and viruses. Computer network security must protect systems that may be internally complicated and perhaps distributed worldwide, but failures can arise simply because the enforcer does not stand to benefit from fixing the problem. **Anderson and Moore** (p. 610) describe how ideas from economics can be applied to information security not only to strengthen the resilience of computer systems to attack but also to optimize the design of peer-to-peer systems, program testing, online privacy, and the politics of digital-rights management.

Night and Day, Far Away

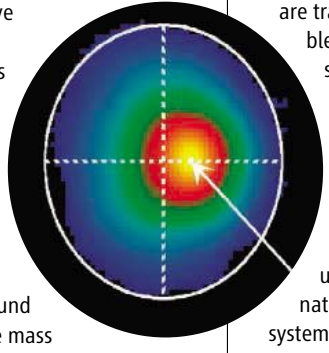
Planets that lie very near their host stars may have a wide differential in atmospheric temperature between the night and day sides. **Harrington *et al.*** (p. 623, published online 12 October; see the cover) report seeing such an effect for the innermost planet orbiting the star υ Andromedae with the Spitzer Space Telescope. They measured the sinusoidal change in the heat of the planet during its 5-day orbit, which indicates that it has distinct hot and cold sides. Because the heat does not spread throughout the atmosphere, the planet's own heat transfer properties can be measured.

Brownian Motion with Twists and Turns

The Brownian diffusion of spherical particles is well understood and goes back to the pioneering work of Einstein and Perrin, but for ellipsoidal particles, the problem becomes much harder because rotational and translational motion are coupling. This problem has been studied theoretically, but the coupling was not directly demonstrated. **Han *et al.*** (p. 626) demonstrate this coupling for a combined theoretical and experimental investigation of ellipsoidal particles, and observe the crossover from anisotropic behavior at short times to isotropic diffusion at long times.

Flaring Disk

Disks that form around young stars provide the sites for later planet formation. In stars that are more massive than the Sun, and correspondingly brighter, it has been argued that flared disks or shells of material may form instead. **Lagage *et al.*** (p. 621, published online 28 September; see the Perspective by **Telesco**) have detected a flared disk around the star HD 97048, whose mass is two and a half times that of the Sun's mass. By modeling the flared disk, they can measure the amount of dust and gas in the disk and suggest it may be a precursor to a debris disk. Planet formation may be difficult in this disk by gravity alone, but some planets may have formed in its inner regions.



Oceanic Birth

How did amino acids form in the prebiotic and hence pre-enzymatic world? **Huber and Wächtershäuser** (p. 630) show that iron and nickel particles can catalyze formation of α–amino and α–hydroxy acids by hydration of methyl thiolate and/or cyanide in basic aqueous solution with high-pressure CO when heated to 100°C. The authors argue that these conditions could have been provided in underwater volcanic vents on the early Earth. The results are consistent with a model whereby coordination of these and more complex organic reduction products to the metal centers progressively gave rise to Fe and Ni-containing hydrogenase enzymes.

Dangerous Hitchhikers

Some hazardous radionuclides in nuclear waste are transported in groundwater not as soluble ions but bound to small, nanometer-scale particles known as colloids. But the nature of likely colloids and the degree to which plutonium may be transported has been uncertain. **Novikov *et al.*** (p. 638) resolve both of these questions at a major waste site in Russia, where plutonium salts used for reprocessing have contaminated a lake connected to a groundwater system. After 55 years, plutonium is now present about 4 kilometers away, bound to iron-oxide colloids.

Formation of Ion Channel Complexes

Large-conductance Ca^{2+}- and voltage-activated K^+ (BK_{Ca}) channels play diverse and critical roles in a number of neuronal functions and provide a link between membrane potential and intracellular calcium. Previous studies suggested a tight functional coupling between BK channels and certain classes of voltage-gated Ca^{2+} channels in

Continued on page 563

CREDITS (TOP TO BOTTOM): ANDREW SWANSON/MANATEE COMMUNITY COLLEGE AND FREDERICK SPIEGEL/UNIV. OF ARKANSAS; LAGAGE *ET AL.*

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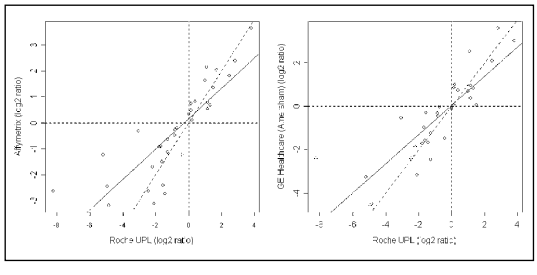

Pairwise scatter plots of UPL qRT-PCR versus microarray measurements (Affymetrix and GE Healthcare). RNA levels for a total of 35 unique genes were quantified by qPCR with Universal ProbeLibrary probes and their $\log_2$ ratios were compared to the microarray measurements ($\log_2$ ratios) of the same genes. The regression lines between the median microarray $\log_2$ ratios and the UPL assay $\log_2$ ratios are displayed in blue. The slope of the lines is compressed, indicating a smaller dynamic range for the microarrays. The Pearson correlation coefficients were 0.834 and 0.851, for Affymetrix and GE Healthcare, respectively, indicating relatively good and highly significant concordance.

Data kindly provided by Dr. Winston Patrick Kuo, Harvard Medical School, USA

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Continued from page 561

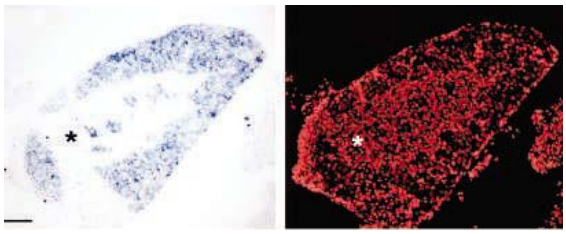
neurons. However, the molecular basis for such coupling has been unclear. **Berkefeld *et al.*** (p. 615) now confirm that BK_{Ca} channels form bimolecular complexes with voltage-gated Ca^{2+} channels. This bimolecular complex formation provides the basis for the fast and localized Ca^{2+} -activated K^+ signaling that controls neuronal firing pattern and release of hormones and transmitters in the central nervous system.

Advancing Honey Bee Biology

Sequencing of the genome of the Western honey bee *Apis mellifera* has recently been completed and has launched a variety of studies aimed at elucidating aspects of honey bee biology and evolution (see the news story by **Pennisi**). **Whitfield *et al.*** (p. 642), reconstructed the relationships among native Old World honey bees (Africa, Asia, and Europe), and present a fine-scale population genetic analysis of introduced New World bees (North and South America). **Wang *et al.*** (p. 645) identified DNA methyltransferase orthologs in the honey bee and demonstrated their catalytic activity. By combining genomic, proteomic, and bioinformatic approaches, **Hummon *et al.*** (p. 647) identified nearly 200 candidate neuropeptides in the honey bee genome, which provides new tools for understanding the neurobiology of this complex social organism. In Brevia, **Poiner and Danforth** (p. 614) describe a 100-million-year-old fossil bee, preserved in amber, along with traces of pollen associated with their role in angiosperm pollination.

Alzheimer's Enzyme and Myelination

β-Secretase activity is crucial in the production of pathological β-amyloid in Alzheimer's disease. However, its role in normal physiology is unclear, especially given the absence of an obvious phenotype in a knockout mouse for BACE1 (beta-site amyloid precursor protein–cleaving enzyme 1). **Willem *et al.*** (p. 664, published online 21 September; see the Perspective by **Glabe**) found that BACE1 (but not its close homolog BACE2) is required for neuregulin (NRG)-mediated peripheral nerve myelination. NRG1 was an in vivo substrate of BACE1, and the BACE-1 knockout mouse fully phenocopied hypomyelination observed in NRG1 heterozygous mutant mice. Thus, BACE-1 plays a physiological role during development in myelination.



CREDIT: WILLEM *ET AL.*

Where Has All the Sulfur Gone?

Marine plankton produce huge amounts of dimethylsulfoniopropionate, which acts as a defensive chemical and osmolyte. One major breakdown product is the gas dimethylsulfide, which contributes to atmospheric aerosol formation at levels that could influence climate. Increasing evidence shows that heterotrophic bacteria in the plankton play an important role in regulating the partitioning of sulfur compounds between the atmosphere and the ocean (see the Perspective by **Malin**). **Howard *et al.*** (p. 649) have surveyed metagenome collections for genes involved in demethylation. In the open ocean, the Pelagibacter are the most important demethylators, but in coastal waters, Roseobacter take over this role. **Vila-Costa *et al.*** (p. 652) show that eukaryotic diatoms and cyanobacteria also act to retain dimethylsulfoniopropionate within plankton food webs. This activity is light-stimulated, seasonal, and appears to involve a sulfur-compound transport mechanism.

Herding Olfactory Axons

In the mammalian olfactory system, sensory neurons each express only one odorant receptor, and the axons from neurons that express the same odorant receptor somehow manage to converge on a single glomerulus in the brain. **Imai *et al.*** (p. 657, published online 21 September; see the Perspective by **Dulac**) have now brought both clarity and complexity to the problem. Although axon guidance was thought to depend solely on the odorant receptor, it now seems that a separate signaling system involving cyclic adenosine monophosphate contributes to guiding axons to a general position along the anteroposterior axis.

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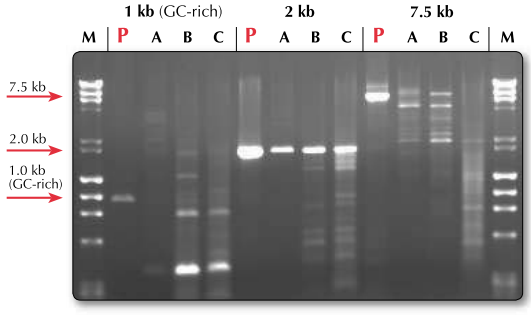

The following fragments were amplified from human genomic DNA: 1kb from CEBPB gene (GC-rich), 2 kb and 7.5 kb from human β-globin gene. Hot start high-fidelity DNA polymerases (P, A,B,C) were used according to suppliers' recommendations:

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Donald Kennedy is the Editor-in-Chief of *Science*.

Why Care About HP?

THE STRANGE TROUBLES AFFLICTING THE HEWLETT-PACKARD COMPANY HAVE BEEN disclosed during the past weeks in one of those agonizingly slow news dribbles. First we learned that agents and perhaps members of the HP board had been impersonating others in order to sleuth out the identity of a director suspected of leaking secrets to the press. Next we were told more than we wanted to know about "pretexting": the dubious and possibly illegal practice through which phone records were being obtained. Then a sting operation designed to trick a reporter into revealing information sources came to light. Finally, though this may not really be the end, the attorney general of California has indicted the former chair of the board and four others for felonious conduct.

Should we care? I think so (disclosure: besides my local Silicon Valley bias, I serve on the board of the David and Lucile Packard Foundation). HP is a major science company; over time, it has developed and produced instruments that can be found in many of our research laboratories. So it's an important entry in the story of science. It's also a company known for the unusual level of social conscience that has accompanied its talent for scientific innovation. Its origin is a Silicon Valley legend that begins with "The Garage": the Palo Alto location to which two young Stanford guys, Dave Packard and Bill Hewlett, took their research interests off campus to begin product development. The lore expanded as the company grew: Both founders had open offices visible on the HP floor, and the "HP Way" became descriptive shorthand for a democratic style of management that was the opposite of imperial CEO-ship. During the company's intense growth phase, Dave Packard regularly served on the Palo Alto School Board, a contribution later interrupted by his service as U.S. Undersecretary of Defense.

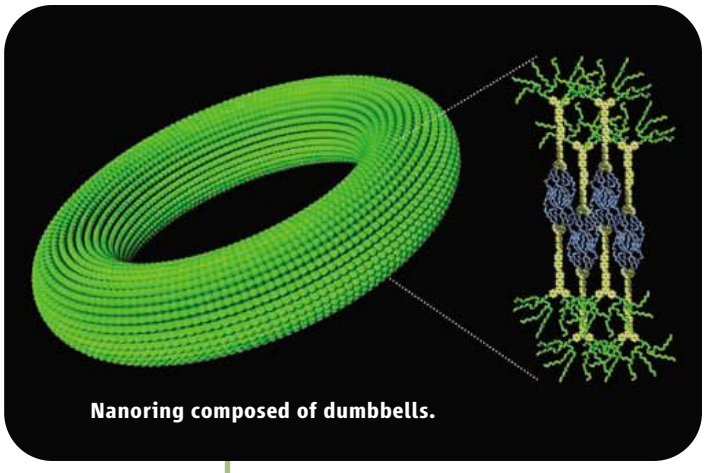
There is something sad about a corporate scandal when it happens to people who have done good things and an organization that has built a treasured reputation over nearly three-quarters of a century. The behavior of some directors was highly questionable and may turn out to be illegal if the attorney general's indictment holds water. Moreover, media and public attention to the problems was surely enhanced by the occasionally bizarre character of the episodes as they unfolded. Granting all that, this case is very different from previous corporate scandals. No one profited, no shareholders were defrauded, and no one falsified accounts. In short, this isn't Enron, HealthSouth, or Global Crossing, but in media presentations, that distinction is not as clearly drawn as it might be.

So it is hardly surprising that the HP scandal is generating anxiety and sympathy in Silicon Valley. HP was a prime mover in making the region a receptive haven for good academic ideas that can be taken into startup companies and turned into products for human service. Next-generation Hewletts and Packards have undertaken leadership roles in the two foundations that bear the founders' names and have helped not only local institutions and projects, but also science—including support for young science faculty, climate change research and analysis, and energy policy. There is a lot of good in the history of HP and its successors; one can hope that fair-minded readers of the negative stories will remember that.

But at least this episode leaves us with a valuable lesson. The agonizing day-by-day unrolling of the bad news should have been halted by a prompt disclosure of the whole story, dirty linen and all. How to do this right is often referred to as the Jim Burke strategy, after the president of Johnson and Johnson who dealt with a fatal Tylenol tampering incident in 1982 (capsules laced with cyanide) by immediately announcing a recall, investigating the case, and changing the product. Had HP put the whole story out right away, expressed regret, and fixed matters, it could have spared the company, its family, and its friends much discomfort. But that didn't happen. How hard it is for us to learn from the mistakes of others!

–Donald Kennedy

10.1126/science.1136275



Nanoring composed of dumbbells.

CHEMISTRY

Tuning Toroids

Amphiphilic molecules with rigid-rod cores can form structures such as tubules, ribbons, and vesicles in aqueous solution. These processes are driven largely by the burial of hydrophobic groups, but the final structures often depend on a balance of energetic and entropic effects.

Kim *et al.* have explored structures formed by dumbbell-shaped molecules with an aromatic core and distinct dendrimeric capping groups: on one end a hydrophilic oligoether and on the other a hydrophobic cluster of three alkyl chains, all either 6, 10, or 14 carbons in length. Transmission electron microscopy images show that these molecular building blocks form micelles. In particular, the hexyl-capped dumbbells form spheres and short cylinders, whereas those bearing decyl chains initially form curved cylinders that close to form toroids, a morphology that further isolates the hydrophobic cores. The compound capped by longer tetradecyl chains forms wider and more extended cylinders, a result that the authors attribute to a decrease in interfacial curvature relative to the decyl-capped species. — PDS

J. Am. Chem. Soc. **128**, 10.1021/ja065487b (2006).

APPLIED PHYSICS

Visualizing the Casimir Force

When two perfectly conducting plates are brought close together, fluctuations in the vacuum field give rise to a difference in electromagnetic modes within the gap (which are limited to integral wavelength multiples equal to the gap width) and those outside the plates (which span an essentially infinite range). The resulting pressure difference thereby forces the two plates together. This quantum mechanical effect, termed the Casimir force, is of fundamental interest in its own right, but it is also becoming an important concern in micro- and nanoelectromechanical devices as a limiting factor in their operation.

Experiments to gauge this effect have generally been limited to fairly simple geometries and materials. Petrov *et al.* present an optical technique based on dynamic holographic interferometry. Deformation of a reflective pellicle due to Casimir force variations, induced by the back-and-forth motion of an opposing aluminum-coated lens, is detected as a shift in the phase and diffraction pattern of an output hologram. The setup relies on two-wave mixing of interfering light beams in a photorefractive cobalt-doped barium titanate crystal. Because this technique is sensitive and quite general, it should be useful for studying realistic device considerations, as well as exploring the effects of dielectric properties and conductivity. — ISO

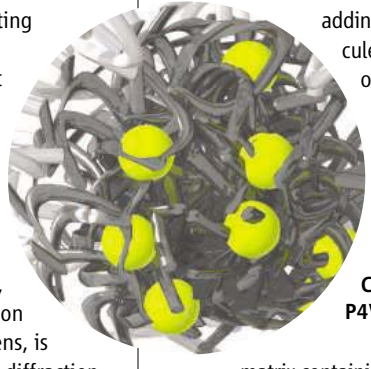
Opt. Lett. **31**, 3167 (2006).

MATERIALS SCIENCE

Pushing Polymers Around

Block copolymers self-assemble into intricately patterned structures because of the tendency for the chemically distinct blocks to segregate. Patterns can be tuned by changing the lengths and interactive properties of the two polymer segments or by adding another component to the mix.

Laiho *et al.* explore the effects of adding fullerene (C_{60}) molecules to a diblock copolymer of polystyrene (PS) and poly(4-vinylpyridine) (P4VP) dissolved in xylene. At the chosen block lengths, the polymer alone formed a PS matrix containing hexagonally ordered P4VP cylinders. Initially, added C_{60} was sequestered in the PS domain, as observed in solution by optical spectroscopy. This localization was mirrored in the morphology of cast films as a reduced abundance of cylinders, indicating that the PS had been swollen by dissolution of C_{60}. However, when the solutions were aged, they underwent the same purple-to-brown color change observed in aging pyridine solutions of C_{60}, consistent with the formation of charge transfer complexes between C_{60} and the electron-donating pyridyl fragments of the P4VP domains. In films cast from these solutions, the P4VP morphology shifted from cylindrical to spherical. The authors suggest that charge transfer complexation is thus a potentially useful tool in designing self-assembled morphologies. — MSL



C_{60} (yellow) clings to P4VP domains (dark gray).

Macromolecules **39**, 10.1021/ma061165g (2006).

IMMUNOLOGY

Vector Protector

As with other vector-borne parasitic diseases, there are two sites at which an immune response might disrupt the lifestyle of the protozoan parasite *Plasmodium falciparum*: in the final host or in its arthropod vector. Indeed, the mosquito is fully capable of generating a robust antiparasitic response against the motile *Plasmodium* ookinete, which invades the insect's midgut to establish itself as an oocyst.

Frolet *et al.* reveal two pathways that contribute to the regulation of this response, presenting evidence that antiparasitic immunity is divided between two phases of parasite invasion. The pre-invasion stage is characterized by basal expression of two effectors: the complement-like thioester-containing protein 1 (TEP1) and

CREDITS (TOP TO BOTTOM): KIM *ET AL.*, *J. AM. CHEM. SOC.* **128**, 10.1021/JA065487B (2006); LAIHO *ET AL.*, *MACROMOLECULES* **39**, 10.1021/MA061165G (2006)

leucine-rich repeat immune protein 1 (LRIM1), which increases in the ookinete invasion stage. The expression of both effectors could be inhibited by silencing the nuclear factor κB (NF-κB) family proteins Rel1 and Rel2, leading to an increase in parasite growth. Conversely, mosquito resistance increased upon inhibition of the IκB-related negative regulator Cactus, leading to high levels of parasite killing. This potent antiparasitic response within the mosquito vector—regulated by the balance between the negative effects of IκB/Cactus and the activation of two NF-κB/Rel transcription factors—could represent a target in the battle against malaria. — SJS

Immunity **25**, 10.1016/j.immuni.2006.08.019 (2006).

CHEMISTRY

Gilding Glucose

The relative inertness of gold has been long been valued for the manufacture of jewelry and other prized items that must resist oxidative tarnishing. Recently, however, homogeneous as well as nanometer-scale colloidal gold has proven increasingly useful in chemical catalysis. Comotti *et al.* explore the potential of gold particles supported on carbon to catalyze the aerobic oxidation of glucose to gluconic acid. Given the relative fragility of this highly functionalized substrate, industrial production of gluconic acid has relied on mild enzymatic methods. A comparison of two aqueous glucose oxidations—one catalyzed by a commercial enzyme preparation and the other by suspended Au/C—shows that under optimized conditions, the gold exhibits comparable activity to the enzymes, requiring only mild heating and vigorous stirring of a basic solution. — JSY

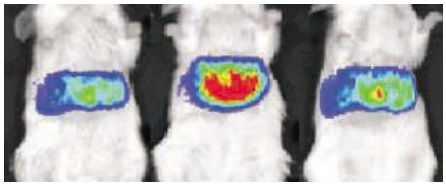
J. Catal. **244**, 122 (2006).

BIOMEDICINE

Starved for Infection

About 600,000 people die each year from hepatitis B virus (HBV)–related liver disease or hepatocellular carcinoma. Recent vaccination programs have been highly effective in preventing new HBV infections, but millions of chronically infected individuals require treatment. Successful therapy development depends in part on identifying host factors in the liver essential for the HBV life cycle.

Working with an HBV-luciferase construct in mice to track viral gene expression in real time, Shlomai *et al*. found that HBV transcription is



Induction of HBV expression in the liver.

tightly coupled to the nutritional state of the animals. Short-term starvation of the mice caused a robust induction of HBV expression that was completely reversible by re-feeding. This effect was dependent on peroxisome proliferator–activated receptor–γ coactivator-1α (PGC-1α), a transcriptional regulatory protein that activates host metabolic genes expressed in response to starvation, including those involved in liver gluconeogenesis. The shared regulation of HBV genes and host metabolic genes suggests that the fluctuating nature of HBV infection may be due not only to mutational changes in the virus but also to changes in the host's nutritional state, a hypothesis offering new possibilities for therapy. — PAK

Proc. Natl. Acad. Sci. U.S.A. **103**, 16003 (2006)

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<< Why a Diet Rich in Seafood is Healthy

Omega-3 fatty acids, which are found in marine organisms, have been associated with beneficial health effects. One mechanism for their anti-inflammatory effect is via competitive inhibition of the enzymatic activity of cyclooxygenase (COX), which is the rate-limiting step in the biosynthesis of prostaglandins. Massaro *et al*. report that exposure of vascular endothelial cells to the omega-3 fatty acid docosahexaenoate (DHA) for periods long enough for it to be incorporated into cellular membranes inhibits the activation of nuclear factor κB (NF-κB) and, subsequently, the expression of *COX-2* and prostaglandin production in response to the proinflammatory signal interleukin-1α (IL-1α). Treatment of endothelial cells with DHA altered their responses to IL-1α by (i) decreasing the activation of extracellular-stimulated kinases 1 and 2, without changing the activation of p38 mitogen-activated protein kinase; (ii) decreasing reactive oxygen species production through inhibiting the membrane association of the $p47^{phox}$ subunit of NADPH oxidase, and (iii) decreasing the membrane association of protein kinase Cε (PKCε), but not PKCα or PKCζ. Thus, it appears that the benefits of omega-3 fatty acids may be due in part to their effects on membrane lipid composition, which reduces signaling in response to inflammatory stimuli. — NRG

Proc. Natl. Acad. Sci. U.S.A. **103**, 15184 (2006).

CREDIT: SHLOMAI *ET AL., PROC. NATL. ACAD. SCI. U.S.A.* **103**, 16003 (2006)

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Information for Contributors

See pages 102 and 103 of the 6 January 2006 issue or access www.sciencemag.org/feature/contribinfo/home.shtml

RESOURCES

GOING OUT WITH A BANG

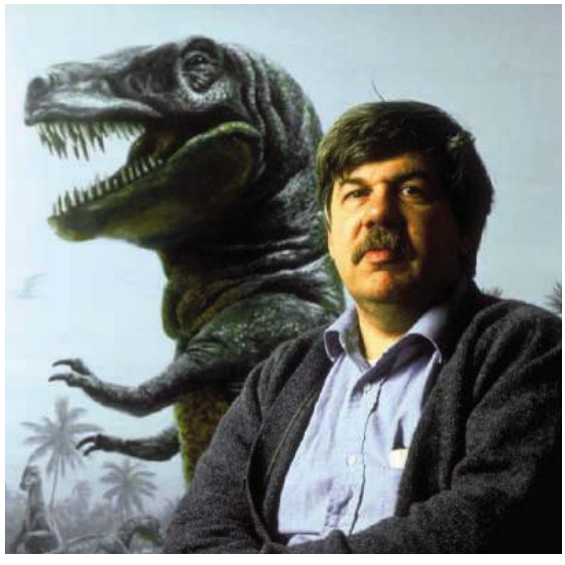
The flash beneath the galaxy NGC 4526 in this 1994 photo is a detonating star. For a roundup of stars that ended their lives explosively, zoom in on the International Supernovae Network* from David Bishop, a computer chip designer and astronomy buff in Rochester, New York. Bishop combs International Astronomical Union reports and other sources to compile the latest and brightest stellar blowups. The listings not only offer observing targets for amateur sky watchers but also supply information useful for professionals, including images, links to spectra, and references.

A supernova usually fades within weeks or months, but its remains linger. For a no-frills catalog of so-called supernova remnants, check this site† from astrophysicist David Green of the University of Cambridge in the U.K. >> * **www.supernovae.net/isn.htm**
† **www.mrao.cam.ac.uk/surveys/snrs**

RESOURCES

This View of Gould

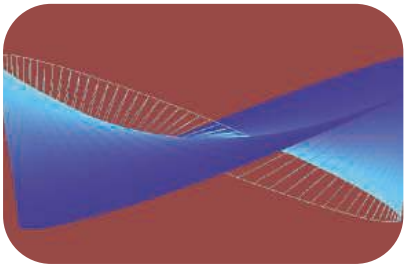
As an essayist, Stephen Jay Gould (1941–2002, below) elegantly elucidated the intricacies of evolutionary theory while citing everyone from Darwin to Joe DiMaggio. As a scientist, he was one of the originators of the punctuated equilibria hypothesis, which states that evolution runs in fits and starts, not smoothly. To sample Gould's oeuvre and bone up on evolutionary thinking, click over to the Unofficial Stephen Jay Gould Archive, hosted by undergraduate Miguel Chavez of Yuba College in California. The site's library brims with writings by Gould and others that tackle some of his favorite subjects, including the levels at which natural selection acts, creationism, and the controversy over intelligence testing and heredity. The multimedia section houses audio interviews with Gould and numerous other evolutionary bigwigs. You'll also find reviews of Gould's works and links to full-text versions of some of his books. >>
www.stephenjaygould.org



EDUCATION

Mix-and-Match Chemistry

Instead of synthesizing and testing compounds one at time, drug designers now often create lineups of slightly varying molecules for faster evaluation, a method called combinatorial chemistry. To unlock the secrets of this approach to drug discovery, browse this primer from Oleg Larin of the Moscow State Academy of Fine Chemical Technology in Russia. The site's six brief chapters explore how researchers perform combinatorial chemistry in the solid phase and in solution. Readers can delve into the different resins for cradling molecules and compare various tags for tracking synthesis products. The site also features a glossary and a collection of combinatorial chemistry articles. >>
www.combichemistry.com



EDUCATION

<< Bent Into Shape

The National Curve Bank, hosted by two mathematicians and a computer scientist at California State University, Los Angeles, is a hall of fame for geometrical figures. The more than 60 pages—many contributed by site visitors—explore curves that have vexed and intrigued mathematicians, such as the conchoid of Nicomedes, a shell-like shape developed in the 3rd century B.C.E., and the familiar Möbius strip (above). This twisted loop defies expectations because it has only one surface instead of a top and bottom. The features also offer historical background about the discoverer and include animations or Java applets. >>
curvebank.calstatela.edu/home/home.htm

WEB PROJECTS

A Scholarly Wikipedia?

A Wikipedia co-founder-turned-detractor is hoping to build a more academic alternative to the freewheeling, user-written encyclopedia. Headed by Larry Sanger, the Citizendium will rely on public participation but will recruit experts to edit entries. Although these editors won't dictate the content of the articles, they will guide authors and referee disputes among them. They can also stamp articles they've vetted as approved. Answering a frequent criticism of Wikipedia, anyone who wants to edit an entry on a scholarly topic will usually need academic credentials. A pilot project to test the strategy began last week. The results won't be open to the public, but you can apply to be an editor or one of the "constables" who enforces the rules. >> citizendium.org

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CREDITS (TOP TO BOTTOM): NASA/ESA; STEVE LISS/GETTY; CALIFORNIA STATE UNIVERSITY, LOS ANGELES


This mom and her blind son both raise their right eyebrows when concentrating.

<<FAMILY RESEMBLANCE

In his 1872 book *The Expression of the Emotions in Man and Animals*, Charles Darwin related the tale of a man with a habit of raising his right arm while asleep and letting his wrist fall heavily on his nose. Years after the man's death, his son was found to do the same.

There are many such anecdotal reports of gestures or facial expressions shared by family members, but researchers in Israel have now done a study showing that characteristic facial expressions run in families, ones even shared by blind people. The results, published online this week in the *Proceedings of the National Academy of Sciences*, suggest that such expressions are under genetic control.

Evolutionary biologists at the University of Haifa at Oranim studied 21 congenitally blind people from different families, as well as one or two sighted relatives of each. Through techniques such as asking subjects to relate personal experiences, the researchers provoked 43 facial gestures covering six emotional states: sadness, anger, disgust, joy, surprise, and concentration.

To gauge family similarity, the researchers carried out an exercise that study co-author Daniel Keren compares to finding the strongest individual in two rope-pull teams. The team used computers to analyze an individual blind person's facial expressions and compare them to those of two groups of 10 families each: one containing the family members and one without. The researchers found that the subjects were matched with the correct group 80% of the time, leading them to conclude that there is a "family facial expression signature." The correct classifications were highest for people showing anger, indicating a particularly high heritability for this expression. In contrast, the researchers found less family resemblance for joy and sadness.

The study is "a very creative attempt to get at the genetic underpinnings of facial expressivity," says psychologist Nancy Segal, a twin researcher at California State University in Fullerton.

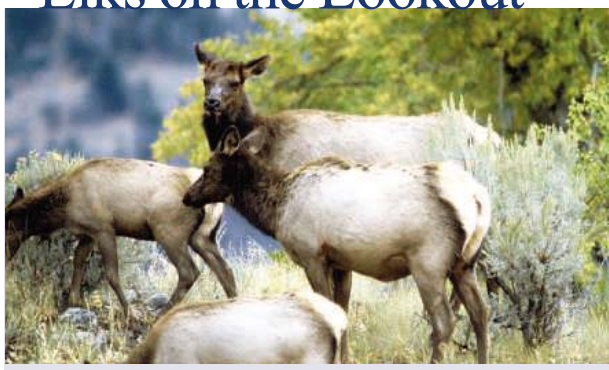
THE WAY THE BALL BOUNCES

Some players in the U.S. National Basketball Association (NBA) hate the new synthetic ball the league adopted this year, and a physicist has agreed to find out whether it really is different from the old leather-covered ball.

NBA players complain that the new ball is slippery and bounces unpredictably. League officials counter that the new ball is more consistent and more durable than the old ball. At the request of the Dallas Mavericks team, Kaushik De, a particle physicist at the University of Texas, Arlington, and colleagues are testing both balls.

De says that his very preliminary results suggest that a worn leather ball bounces higher than the synthetic ball, although the synthetic ball and a new leather ball bounce about equally. A worn leather ball also bounces truer than a new leather ball, which has deeper grooves and is embossed with logos, he says. Perhaps most important, the new synthetic ball does not absorb water, which means it gets slippery when wet. A leather ball absorbs moisture and actually gets stickier, De says. He notes that the ball's manufacturer, Spalding, designed it not to absorb water so as to maintain a constant weight: "In optimizing one variable, they seem to have affected the others."

Elks on the Lookout



A wolf pack can take down four elks a week. But male elks don't seem too concerned: They let females keep tabs on these predators. Indeed, males bother to look around only when they are worried about being cuckolded, says Mark Lung, a wildlife biologist at Western State College in Gunnison, Colorado.

Lung and Michael Childress, a behavioral ecologist at Clemson University in South Carolina, used the 1995 introduction of wolves into northern Yellowstone National Park as a natural experiment assessing how the predators affect elk behavior. Over several springs, they tracked how often elks in herds in different locations in the park—and consequently, with varying exposure to wolves—stopped feeding to look around. This vigilance is thought to be a common antipredatory behavior. But when wolves came within sight of the herd, the males seemed oblivious, and it fell upon the females to prod browsing comrades to move to a safer spot. "Males didn't pay any attention to the increased risk at all," says Childress.

During the fall, however, male elks spend quite a lot of time scanning their surroundings. But it's other males, not predators, that grab their attention, Lung and Childress reported online last week in *Behavioral Ecology*. That's likely because fall is the rutting season, a time when males cordon off as many females for themselves as possible. The nonchalance to predators—males will also ignore a grizzly bear, whereas a female quickly leaves—and obsession with sex are all part of the male elk psyche, says Childress: "It's a live-fast-and-die-young strategy."

CREDITS (TOP TO BOTTOM): PELEG *ET AL.*/PNAS; PHOTOS.COM; SPALDING

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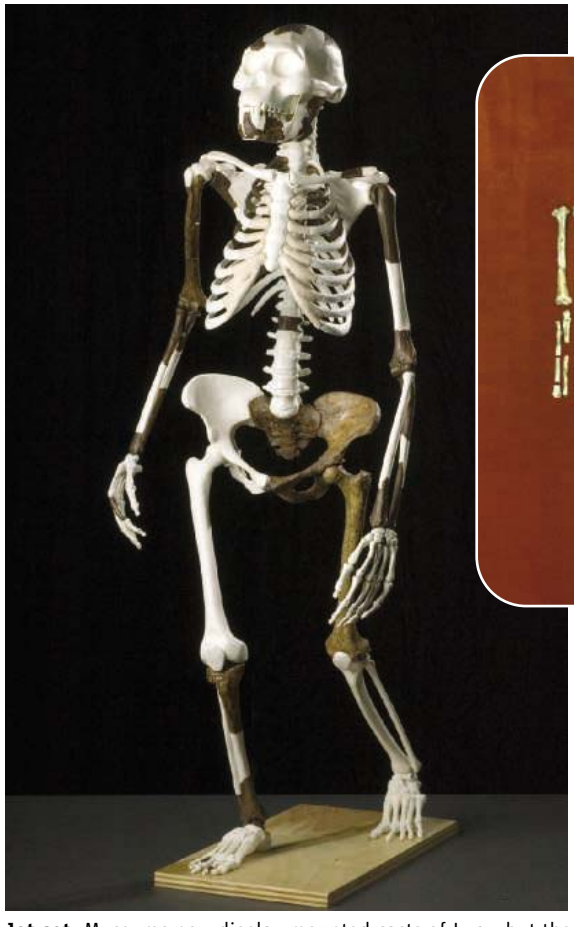
PALEOANTHROPOLOGY

Lucy's Tour Abroad Sparks Protests

The famous human ancestor Lucy probably lived and died within a short distance of her burying ground at Hadar, Ethiopia, after a short, obscure life. Now, 3.1 million years after her death, Lucy is headed for her first public appearance ever at a museum in Texas, where her status as a paleo–rock star is expected to draw large crowds. After 4 years of talks, officials signed a multimillion-dollar contract Tuesday to fly the original partial skeleton to the Houston Museum of Natural Science for an exhibit in fall 2007, says museum archaeologist Dirk Van Tuerenhout.

Ethiopian officials have high hopes that Lucy will do for Ethiopia what King Tut's riches did for Egypt. "It will put Ethiopia on the map as the cradle of mankind and of civilization," says Mohamoud Dirir, Ethiopia's minister of culture and tourism. The culture ministry is planning a lengthy tour for Lucy, with stops at 10 museums and a homecoming in 2013.

But many of the people who know Lucy best—leading researchers in the United States and Africa—are fighting to stop her posthumous tour, saying that transporting and exhibiting the fragile, one-of-a-kind specimen could damage it. They have protested to African politicians and American museum officials that Lucy's travels are unlikely to benefit Ethiopian science, and that the exhibit would violate a 1998 UNESCO agreement against transporting original hominids out of their home countries. Such concerns have prompted several leading museums to turn down the exhibit. "There is only one Lucy," says Bruce Latimer, director of the Cleveland Museum of Natural History in Ohio. "If something should happen to her, she's irreplaceable."



Jet set. Museums now display mounted casts of Lucy, but the original relics (*inset*) are to be flown to a museum in Houston, Texas, and perhaps others.

They are not concerned only about Lucy. Her travels may pave the way for other rare hominids to journey overseas. For example, Kenyan officials are in discussions with the Field Museum in Chicago, Illinois, about exhibiting the 1.6-million-year-old Nariokotome Boy, the only published skeleton of *Homo erectus*. Lucy's tour "will start an avalanche," grimly predicts paleoanthropologist Clark Howell of the University of California, Berkeley. "We'll fight this thing when it appears on opening day and afterward."

Many museums already feature Lucy, a key ancestor whose bones first revealed that our lineage walked upright before evolving a big brain. But all exhibits use casts: The original fossils have never been on display. They have been out of Ethiopia only once before, in 1975, when discoverer Donald Johanson took them to the Cleveland Museum for study and baptized Lucy as a new species, *Australopithecus afarensis*.

Johanson returned the bones to Ethiopia in 1980. At that time, African nations were reclaiming fossils that had been shipped around the world and making them centerpieces of museums and fledgling research programs. Keeping original fossils in Africa was part of a strategy for boosting homegrown science. "If we start sending these fossils out of the country, Kenya and Ethiopia cease to be places where you can study fossils. It immediately changes the role of the museum as a place for scientific study," says Kenyan paleoanthropologist Richard Leakey, former director of the National Museums of Kenya. Paleoanthropologist Bernard Wood of George Washington University in Washington, D.C., puts it more starkly: Without the fossils, "why would anybody want to [work in] Ethiopia or Kenya? Why would anybody want to develop the science base or train the people?"

That's part of the reason why, in 1998, three dozen scientists from 23 nations signed an international agreement not to transport original hominid fossils from their homelands except for compelling scientific reasons. Now, however, persistent economic woes have prompted government officials in Ethiopia and Kenya to revisit the idea. Ethiopian officials say that spreading the word about Lucy and their nation's rich cultural heritage can help draw tourists to Ethiopia and change its image. "The money will go to museums, and just to museums," says Dirir. "Just keeping fossils in Ethiopia will not develop science, museums, or the custodians of these fossils."

CREDITS (MAIN AND INSET): THE CLEVELAND MUSEUM OF NATURAL HISTORY

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Houston plans an exhibit that will include an overview of Ethiopian history from 5 million years to the present. Van Tuerenhout asked for other, unpublished fossils, including those of the even older hominid *Ardipithecus*, but Dirir said those will not go.

It is Lucy, however, whose box-office appeal is critical for the Houston exhibit's success, Van Tuerenhout says: "Lucy has name recognition. That is especially important with schoolchildren. You can show them this is what evolution is about."

John Kappelman of the University of Texas, Austin, who is developing teaching materials on Lucy for children and plans to do state-of-the-art computed tomography scans of the fossils, predicts that if the show travels to other venues, "millions of Americans will look at this original material. That could change the way many people think about human evolution," including helping to defeat creationism.

To draw in the masses, Van Tuerenhout and Kappelman say they need the original fossil. They point out that few crowds would line up to see replicas of the Mona Lisa or the Hope diamond, for example. That's why security for Lucy will need to be as good as it is for the genuine Hope diamond, with guards, insurance, and trained handlers, responds Richard Potts of the Smithsonian Institution. He agrees with the UNESCO policy, saying that extended exhibition is not worth the risk unless the bones need to be moved for compelling research purposes.

Van Tuerenhout says Houston will provide whatever security measures the Ethiopian ministers seek; the ministers are dictating those details, he says, from Lucy's first-class seat on Ethiopian Airlines to the fossils and artifacts that accompany her.

Houston is to be the first stop on a longer tour to musums in New York, Chicago, and Washington, D.C. But none of those museums have plans to sign on as yet, and the Smithsonian and the Cleveland Museum have explicitly said no. The nonprofit Leakey Foundation, which funds anthropological research, considered sponsoring the exhibit but decided against it last year after passionate protest from its scientific executive committee, says Leakey Trustee Don Dana, a vice president of Wells Fargo Bank. Some trustees also were concerned because the Houston Museum would not divulge details of its financial arrangements with Ethiopia. "You want to avoid a situation where you're buying someone a Land Rover," says Dana.

Ethiopian scientists say it's not yet clear to them where the loan fees from Lucy will go. "What Ethiopians are benefiting from this?" asks Ethiopian paleoanthropologist Zeresenay Alemseged of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. "I have not seen a document that clearly defines the role for the National Museum of Ethiopia. I have never heard of any Ethiopian paleoanthropologist being involved. If money is being generated, it should be clear what percentage will go to Ethiopian science."

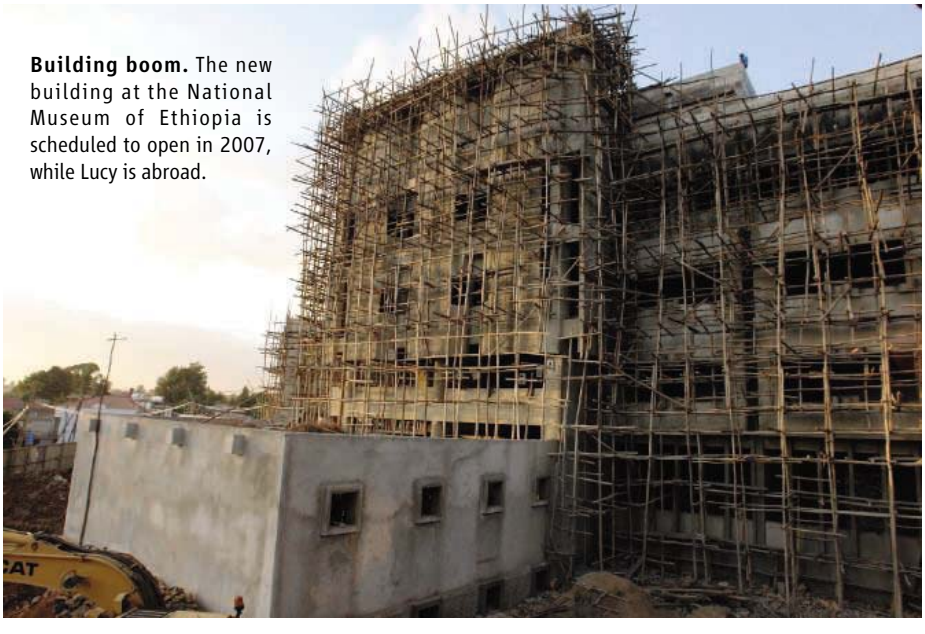
Houston officials bristle at the suggestion that they tell Ethiopian ministry officials how to spend their money, but other museums do restrict the use of loan fees. For example, National Geographic Society Vice President Terry Garcia says that he explicitly required that fees paid to Egypt for the new King Tut exhibit be used to advance archaeology.

Lucy's impending visit is a test case that has "started a conversation at museums," says paleontologist Neil Shubin, provost of the Field Museum. After a visit to the Field in September, Kenyan officials surprised museum officials with an announcement that fossil hominids, including the Nariokotome Boy, would be exhibited there, says Shubin. "We had not even vetted the idea with our board," he says; he was immediately lobbied by prominent scientists opposed to the idea.

Shubin says talks are preliminary, but the director general of the National Museums of Kenya, Idle Omar Farah, is optimistic: "Our initial verbal conversations appear to indicate that we could have some selected collections of our hominid fossils traveling to the Field Museum, but the form, composition, and time is as yet to be determined." Farah says loan fees would be used to set up an endowment for the museum, and the interest would be spent on collections and staff. He has had inquiries from Germany, Switzerland, the United Kingdom, and Japan, if the Field passes.

Kenyan paleontologists, however, oppose such displays. "I do not support displaying of our precious fossils in any [other] museum regardless of what funds it would attract," says Emma Mbua, head of paleontology at the National Museums of Kenya. "These fossils are our pride and strength as a country. Displaying them anywhere else than our own museum is not right."

Meanwhile, both Kenya and Ethiopia are rebuilding their museums. Ethiopia's National Museum is getting a new, five-story building scheduled to have its grand opening in 2007—when its star attraction is out of town. **–ANN GIBBONS**



Building boom. The new building at the National Museum of Ethiopia is scheduled to open in 2007, while Lucy is abroad.

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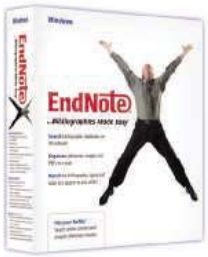

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OCEAN DRILLING

Higher Costs, Accident Imperil Plans

The Integrated Ocean Drilling Program (IODP) has hit rough waters. A spike in the demand for oil-drilling equipment and services has added 20% to the cost of a planned extreme makeover of the program's former workhorse, the drill ship *JOIDES Resolution* (*Science*, 23 December 2005, p. 1890). By happenstance, the funding squeeze comes as the program's future flagship, the new Japanese drilling ship *Chikyu*, sustained damage to one of its key drilling components during a shakedown cruise off the Japanese coast. "It's tough going at the moment," admits Bill Ball of the Joint Oceanographic Institutions, which is managing the modernization of the *JOIDES Resolution* for the U.S. National Science Foundation (NSF).

IODP's predecessor, the Ocean Drilling Program, was for 2 decades the world's premier effort to explore beneath the sea floor (*Science*, 18 April 2003, p. 410). In 2003, the U.S., European, and Japanese members of the consortium reorganized the program and began preparing for the arrival of the $550 million *Chikyu*, which is equipped with a second pipe, called a riser, that allows it to drill deeper holes and in areas near oil and gas deposits (*Science*, 11 March 2005, p. 1552). Both the *Chikyu* and the renovated ship, which NSF leases from an oil-drilling company, were to begin scientific drilling in the fall of 2007.

That schedule now appears impossible to meet for the refurbished ship. For $115 million the NSF vessel, which will be renamed, was to get a 30-foot hull extension that provides 50% more lab space and bigger and better accommodations. The ship is also slated for enhanced instrumentation and drill capacity and faster, more fuel-efficient operations. Now NSF officials must figure out how to either get the most for the budgeted amount or pay for the $25 million overrun by cutting back on another big-ticket construction item. "Any increase has to come from the major research equipment and facilities account, not from the research account," explains Margaret Leinen, head of NSF's geosciences directorate.

The clock is ticking as NSF awaits a report on how much can be done to improve the ship's capabilities without stretching the hull. The renovations were supposed to have gotten under way this month at a facility in Singapore, and NSF is paying tens of thousands of dollars each day the ship is tied up. Although work can begin on improvements unrelated to the extension, Leinen stresses that NSF must make a decision "as soon as possible." In the meantime, she says "we definitely won't be making" the target date of November 2007 to resume operations.

Still standing. The crew of the *Chikyu* hopes to repair a storm-damaged part of its drilling equipment while at sea.

CREDIT: JAMSTEC

As for the *Chikyu*, officials at the Japan Agency for Marine-Earth Science and Technology (JAMSTEC) are hoping to fabricate or buy a replacement for a rod that's part of a device to prevent blowouts when the ship drills into a volatile formation. It got bent when the ship was caught in a sudden storm earlier this month with its drilling equipment deployed. Asahiko Taira, director-general of JAMSTEC's Center for Deep-Earth Exploration, says the damage is minor and the bent rod will be replaced at sea.

The *Chikyu* must then rush off to drill for oil off the coast of eastern Africa. Taira says the commercial job will allow the agency to meet rising operating costs while still training the crew and gaining drilling experience in various geologic environments. "We will have this ship ready for scientific drilling in September next year," he vows. **–JEFFREY MERVIS**

With reporting by Dennis Normile in Tokyo.

Don't Catch Some Rays

With plans for 6-month moon missions, NASA needs to look harder at the effects of radiation on astronauts, their spacecraft, and their lunar base. That's the conclusion of a new report from the National Academies' National Research Council (NRC), which warns that the radiation could damage astronauts' bodies as well as electronic equipment on board. Rather than trying to solve the problem by over-designing a moon base with too much shielding—an expensive prospect—NASA could save money by determining the extent of the threat through existing data sets and tools regularly used by solar and space physicists. The NRC panel urges human-space-flight planners and radiation researchers to work together.

–ANDREW LAWLER

Sicily Center Iced

Italy's new budget zeroes out a $410 million Biomedical Research Center in Palermo, Sicily—a joint project planned with the University of Pittsburgh Medical School for studies of regenerative medicine, medical imaging, and computational biology (*Science*, 14 April, p. 177). Funding was promised by former prime minister Silvio Berlusconi, who was defeated in the April national election. Recruitment for a staff of 600 was well under way when word arrived this month that the government will back out, says Bruno Gridelli, director of the ISMETT organ-transplantation research center in Palermo, which was to host the project. The cancellation, he says, "represents a substantial loss" for Sicily. Now the medical school will look for other partners.

–JACOPO PASOTTI

Chinese Genomicists Target Cancer

The $10 million Cancer Genome project, announced last week, marks China's first large-scale research program targeting a specific clinical disease. The program focuses on variations at the structural genomic and sequence levels, epigenomics, and transcriptomics, says Yang Huanming, director of the Beijing Genomics Institute. The program will carry out research into cancers that are prevalent in China, which could include lung, liver, stomach, and esophageal cancers. U.S. National Cancer Institute official Daniela Gerhard calls the project "a good idea," noting China's unique tumor samples. Although China is a partner in the international Human Genome and HapMap projects, Gerhard says the United States will wait for more details before considering partnering on the latest effort.

–GONG YIDONG

GENETICS

Honey Bee Genome Illuminates Insect Evolution and Social Behavior

Four years in the making, the 236-million-base genome of the European honey bee, *Apis mellifera*, proved tough to decipher. But the hard work paid off this week as 170 researchers rolled out their analysis of this fifth insect sequenced to date. "To have [this] genome laid out in some detail is a real step forward for our understanding of this part of the animal kingdom," says Francis Collins, director of the National Human Genome Research Institute in Bethesda, Maryland, which funded the sequencing work.

The honey bee genome, described in the 26 October issue of *Nature*, has inspired dozens of recent papers in several journals, including three this week in *Science*. The 10,157 genes identified so far contain clues about the social behavior, physiology, and evolution of the honey bee, as well as insights into other insects and even vertebrates. The sequence also promises to illuminate the genetic and neural basis of animal social behavior. "It's the understanding of behavior that's going to be the big payoff [of the honey bee genome]," predicts George Weinstock, the geneticist at Baylor College of Medicine in Houston, Texas, who led the sequencing effort.

Bee hives are organized around an egg-laying queen tended by workers who, during their lifetime, make the transition from hive-bound duties, such as nursing larvae, to more far-ranging jobs such as foraging for food or defending the nest. With just a million neurons, the bee brain is relatively simple, yet these insects are sophisticated—for example, they use highly choreographed "dances" to communicate the location of nectar-laden flowers.

With the aid of the genome data, Gene Robinson, a neurobiologist at the University of Illinois, Urbana-Champaign (UIUC), has begun to tease apart the genetic and environmental components of the bee social structure and its related behaviors (*Science*, 10 October 2003, p. 296). Now, working with Charles Whitfield, a geneticist also at UIUC, Robinson has used microarrays to determine which of 5500 genes are active in young bees and which are affected by age-related changes in juvenile hormone, a key mediator of behavioral maturation. Those results appeared online 26 October in the *Proceedings of the National Academy of Sciences* (*PNAS*).

Two other studies, one reported in the same *PNAS* issue and another in *Science*, begin to address what turns the bee's behavioral genes on and off. On page 647, Robinson's UIUC colleague Saurabh Sinha has picked out some of the regulatory regions that control some 3219 genes in the bee's brain, including ones important for the development of foraging behavior. And on page 645, Ying Wang in Robinson's lab and their colleagues report that unlike other insects studied, the honey bee has a vertebrate-like set of enzymes needed to methylate genes, implying that methylation may be important in silencing genes in bees as well as in vertebrates, including humans. "For people interested in human behavior, their interest [in the honey bee] has just gotten supercharged," says Collins.

Minding the hive. The social nature of honey bees, with workers that tend larvae and an egg-laying queen, makes the species' genome alluring.

Meanwhile, evolutionary biologists are keen to compare the honey bee genome to those of the six-legged lab rat of the insect world—the fruit fly—the mosquito, and the silkworm. "We are poised to sketch out the beginnings of genomic evolution in the insects, a not-trivial slice of the diversity of life," says Brian Farrell, a Harvard entomologist at the Museum of Comparative Zoology in Cambridge, Massachusetts. Moreover, a new bee fossil found in 100-million-year-old amber, reported on page 614, should clarify how honey bees evolved from predatory wasps and became key pollinators. The fossil, and the pollen captured with it, are "enabling us to place a time frame on this genomic evolution," Farrell adds.

These new genomic analyses suggest that bees and their wasp relatives, the so-called Hymenoptera, had an earlier-than-expected evolutionary start. In one study, Joël Savard and Martin Lercher of the University of Cologne, Germany, and colleagues compared 185 genes from the honey bee, fruit fly, mosquito, flour beetle, parasitic wasp, and silkworm. They concluded that the Hymenoptera branched off quite early from the line of so-called holometabolous insects, those that undergo complete metamorphosis. This wasp-bee branch predates that of the beetles, contrary to prevailing dogma, Savard and Lercher argue in the November issue of *Genome Research.*

Genomics studies are tracing the roots of bees in general, and honey bees in particular, to Africa. In one, published in the 6 October issue of *PNAS*, bee systematist Bryan Danforth of Cornell University published a new family tree for bees, which are 16,000 species strong. He not only analyzed morphological data but also used five genes from the honey bee genome as a way to track down those same genes in 80 bee species and 14 wasps. The primitive bee lineages are most diverse in Africa, indicating that's where this group likely arose, he concludes.

In the other study, Whitfield sorted out the radiation of the relatively late-evolving honey bees. Although Harvard entomologist Edward Wilson suggested 35 years ago that the honey bee first called Africa home, most researchers had concluded that this insect hails from Asia, as that's where the rest of the *Apis* genus is found. By analyzing 1500 single-nucleotide polymorphisms (SNPs)—differences of a single DNA base—Whitfield and his colleagues confirmed that four clusters of honey bee subspecies, as originally defined through mitochondrial DNA studies, exist: two in Europe, one in Asia, and one in Africa. (Subsequently, there have been multiple introductions of various subspecies by humans into the New World.)

The SNP data reveal how these clusters arose from two "out of Africa" migrations, Whitfield and his colleagues report on page 642. In one, bees landing in Spain moved into central Europe and Russia. In another, bees colonized eastern Europe south of the Alps and then expanded into Asia. As a

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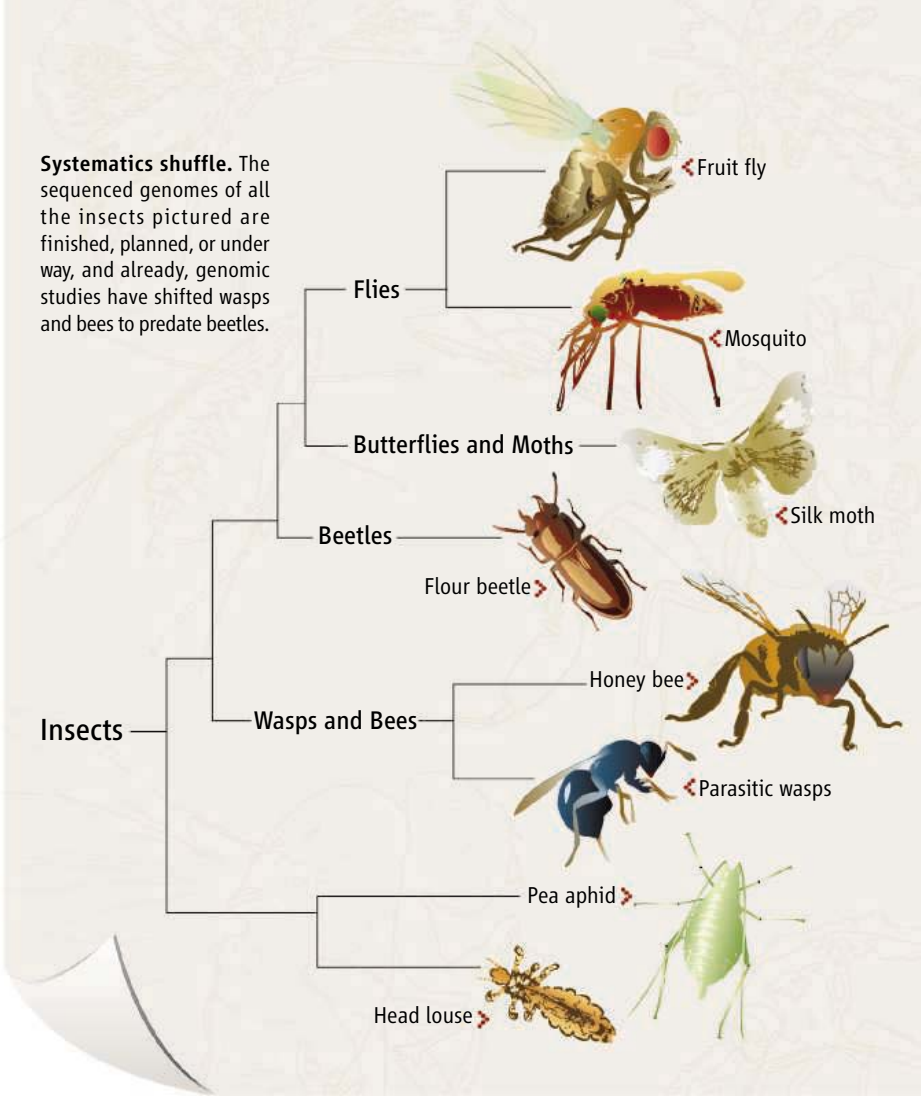


Systematics shuffle. The sequenced genomes of all the insects pictured are finished, planned, or under way, and already, genomic studies have shifted wasps and bees to predate beetles.

CREDIT: (ILLUSTRATION) N. KEVITIYAGALA/*SCIENCE*; (SOURCE) ADAPTED FROM *NATURE*

result, despite their geographic proximity, "the two European groups are the most different on Earth," says Whitfield.

Compared to the fruit fly and the mosquito, the honey bee has evolved at a glacial pace, Weinstock and colleagues report in the 26 October *Nature* paper. But compared to those two insects, certain gene families essential to the bee's social lifestyle have expanded in size. In the November issue of *Genome Research*, Hugh Robertson and Kevin Wanner of UIUC report about 165 odorant-receptor genes in the honey bee genome, more than double what *Drosophila* and *Anopheles* have. This expansion makes sense, says Robertson, given the bee's need to recognize kin and find suitable flowers. Honey bees also have multiple versions of a pigmentation gene, called *yellow protein*, that have been co-opted to make royal jelly, a nutrient-rich secretion that causes larvae to develop into queens, Ryszard Maleszka of Australian National University in Canberra and his group report in the same issue of *Genome Research.*

In a few respects, the honey bee shares more similarities with humans than with the other insects whose genomes have been sequenced. It retains some 700 genes found in other organisms, such as nematodes, yeast, or mammals, that the fruit fly and mosquito have lost. Those genes are presumably ancient, found in the common ancestor of all the creatures and then lost in a few lines. Take some of the genes that drive the biological clock behind circadian rhythms. The honey bee has several clock genes that closely resemble mammalian clock genes yet are missing in fruit flies, says Guy Bloch of The Hebrew University of Jerusalem, Israel. At the same time, the honey bee lacks two of the fruit fly's clock genes, says Bloch. *Drosophila* apparently grew to depend on one subset of an ancient cluster of clock genes, whereas bees and mammals depend on another.

Dozens of other findings have come out of this first round of exploration into the honey bee genome, says Weinstock. Still, he's most excited about the long-term effect of this massive endeavor. "It's very gratifying to see the biology coming alive right away. [But] it's more than just teasing the biology out," Weinstock says. "It's getting the whole community up to speed in genomics."

–ELIZABETH PENNISI

SCIENCESCOPE

Blocked Cancer Study Published

A study of cancer death rates among U.S. computer-chip workers was published last week after IBM lost its legal battle to block the author from publishing it. Epidemiologist Richard Clapp of Boston University analyzed mortality data on 31,941 American IBM employees, many retired, who died between 1969 and 2001. He reported last week in *Environmental Health* that men and women in that group were 7% or 15% more likely, respectively, to have died from cancer than were those in an age- and sex-matched subset of the U.S. population. What's more, men who worked at one of four U.S. chip- and disk-drive manufacturing plants faced significantly higher risks of death from kidney and brain cancer, and, for women, breast cancer.

Clapp did the study after being hired as an expert witness for the former IBM workers who were suing the company (*Science*, 14 May 2004, p. 937). IBM's lawyers argued for almost 2 years that the study could be used only for litigation, but a New York district judge ruled in February that Clapp was free to publish it. "It feels great," Clapp says. IBM spokesperson Chris Andrews says that "Clapp's assertions are not backed by any credible science." Epidemiologist John Bailar, scholar-in-residence at the National Academy of Sciences in Washington, D.C., says that "from what I know at present, there is an excess cancer risk." **–DAN FERBER**

Taking a Shot at Flu

After consulting with more than 120 experts, the World Health Organization (WHO) in Geneva, Switzerland, announced a plan this week to drastically shore up the world's capacity to produce influenza vaccines—a measure that it says could save millions of lives if a flu pandemic strikes. Developing a vaccine that works is one challenge should a pandemic of H5N1 or another flu strain occur. Rapidly churning out enough of the vaccine to protect 6 billion people is even tougher. Currently, flu vaccine companies produce only 350 million doses of the seasonal influenza vaccine per year. That's why the use of annual vaccine should be promoted and new factories built—especially in the developing world—while scientists look for vaccines that are more broadly effective and easier to make, the agency says. WHO is hoping that rich countries will finance the plan, for which it has almost no budget.

"It's good that WHO is at long last speaking up on the production issues," says David Fedson, a vaccine expert and former executive at Aventis Pasteur MSD who follows pandemic vaccine issues closely. **–MARTIN ENSERINK**

EUROPE

Dark-Horse Neutron Source Heads Belatedly Toward Starting Line

Several European governments are lining up behind construction of a high-powered neutron source that would allow the region to keep pace with new facilities in the United States and Japan. The design team for the €1.2 billion ($1.5 billion) European Spallation Source (ESS) was dissolved in 2002 due to lack of interest from potential funders, but supporters point to several recent studies backing the concept for the renewed interest. "There is now a total consensus that the ESS is necessary," says Peter Tindemans, chair of the ESS Initiative, a lobbying group that has been keeping the ESS flame alive.

Big draw. Thousands of researchers want the European Spallation Source, but will politics behind closed doors decide its location?

Neutron beams are used in a wide variety of disciplines, including physics, materials science, biochemistry, engineering, and medicine. Because neutrons lack electrical charge, they can penetrate deep into materials to reveal structure that is invisible to other probes. Some 5000 researchers in Europe use neutron sources, which come in two types: nuclear reactors and spallation sources, accelerators that fire a proton beam at a metal target to create a spray of neutrons. For more than a decade, Europe has been home to both the world's most powerful nuclear reactor source, the Institut Laue-Langevin in Grenoble, France, and the top spallation facility, ISIS, at the United Kingdom's Rutherford Appleton Laboratory near Oxford.

In 1999, the Organisation for Economic Co-operation and Development (OECD) in Paris published an influential report on neutron sources, which recommended that East Asia, Europe, and North America should each build a new high-powered source. The report galvanized efforts for new sources in the United States and Japan. Earlier this year, the Spallation Neutron Source at Oak Ridge National Laboratory in Tennessee produced its first neutrons and is now working up to its full beam power of 1 megawatt. And Japan is building a spallation source as part of its J-PARC proton accelerator complex at Tokai. The 1-megawatt source will produce its first beams in 2007.

European governments, meanwhile, eschewed new construction. It wasn't for lack of scientific interest: A group of European labs had begun design work on ESS in the early 1990s, and in 2002, researchers put forward a final project proposal for a 5-megawatt machine. Five regions expressed interest in hosting it. But with no national governments prepared to foot the bill, the idea languished.

Since then, "there's been a lot of work ▶

SCIENCE AND BUSINESS

DeCODE Adds Plagiarism Allegation to Its Case

Escalating its pursuit of employees who allegedly took trade secrets when they quit, deCODE Genetics in Reykjavik, Iceland, has now accused its former vice president, Hákon Hákonarson, of plagiarism. Hákonarson is one of five former deCODE researchers whom the company sued last month for taking confidential data to set up a competing genetics unit at the Children's Hospital of Philadelphia (CHOP) in Pennsylvania (*Science*, 6 October, p. 30).

Hákonarson, director of the new unit, declined comment to *Science*. But CHOP President Steve Altschuler said in a statement: "DeCODE's claims of research misconduct, like the complaint it filed in federal court against Dr. Hákonarson, are wholly baseless and without merit."

DeCODE makes the new allegations in an 18 October letter to the National Institutes of Health (NIH) and the Office of Research Integrity (ORI) at the U.S. Department of Health and Human Services. The five-page letter, signed by deCODE counsel Thorir Haraldsson and Hreinn Stefánsson, head of the company's central nervous system diseases division, asks U.S. officials to investigate "research misconduct … and take appropriate action." ORI could bar Hákonarson and, in theory, CHOP from receiving U.S. research funds if the charges are found to be true.

Using a document previously filed with the Philadelphia federal court hearing its lawsuit, deCODE's new letter supports its plagiarism case with a side-by-side comparison of texts taken from a 2005 grant application it submitted to the European Union for schizophrenia research and a CHOP proposal for asthma studies, which deCODE claims Hákonarson and CHOP authored and submitted to NIH in April 2006. The comparison highlights more than a dozen passages that are nearly identical. DeCODE charges: "The CHOP grant application contains text taken verbatim from the description … in the deCODE grant proposal." DeCODE also claims that Hákonarson misstated his company credentials in the NIH grant.

In the lawsuit revealed last month, deCODE asked the federal court to prevent its former employees from working with CHOP on its new genetics unit for 2 years. The company claims that Hákonarson and his colleagues downloaded thousands of files from deCODE onto portable hard disks and memory sticks, copied them, and then destroyed some of the equipment to hide evidence. The court has not yet reached a decision on deCODE's request for an injunction. The hearing was suspended earlier this month and is expected to resume on 13 November.

–ELIOT MARSHALL

CREDIT: EUROPEAN SPALLATION SOURCE PROJECT

going on behind the scenes," says physicist Robert Cywinski of Leeds University in the U.K., scientific adviser to an ESS bid from three Yorkshire universities and the regional development organization. In 2003, the Yorkshire team met with U.K. Science Minister David Sainsbury, who ordered up a review of Britain's future requirements for neutron facilities. Published last March, the review didn't endorse ESS but made a megawatt-level spallation source the top priority and urged the government to work with European partners to develop one.

ESS is also one of 35 large-scale projects deemed worthy of support in a report this month from the European Strategy Forum on Research Infrastructures (ESFRI) (*Science*, 20 October, p. 399). ESS could move straight to construction as soon as negotiations on site and funding are complete, the forum concluded. "The ESS has come back with a vengeance in the ESFRI road map," says Cywinski. Tindemans says that both the U.K. neutron review and the road map have "helped enormously."

Physicist Karl-Fredrik Berggren of Linkopings University in Sweden says that the Swedish government last year completed a review and supports building ESS at Lund University. "We expect approval should come fairly shortly," he predicts. At a meeting of the ESS Initiative in Bilbao, Spain, earlier this month, the Basque regional government said the national government would support its bid, along with a rumored €300 million in funding. Tindemans says Hungary is also poised to approve a bid to site ESS on its soil.

Cywinski says the Yorkshire bid is currently in limbo, as the government has not responded to the neutron review. Right now, "governments are just trying to form alliances," says Tindeman. According to Berggren, "The country that ties up the big nations very quickly will win."

With the U.S. and Japanese sources already talking about upgrading the power of their accelerators, to 2.5 and 5 megawatts, respectively, Europe needs to move quickly if it is to keep pace, says Cywinski: "If the focus of neutron science moves from Europe, the scientists will move too."

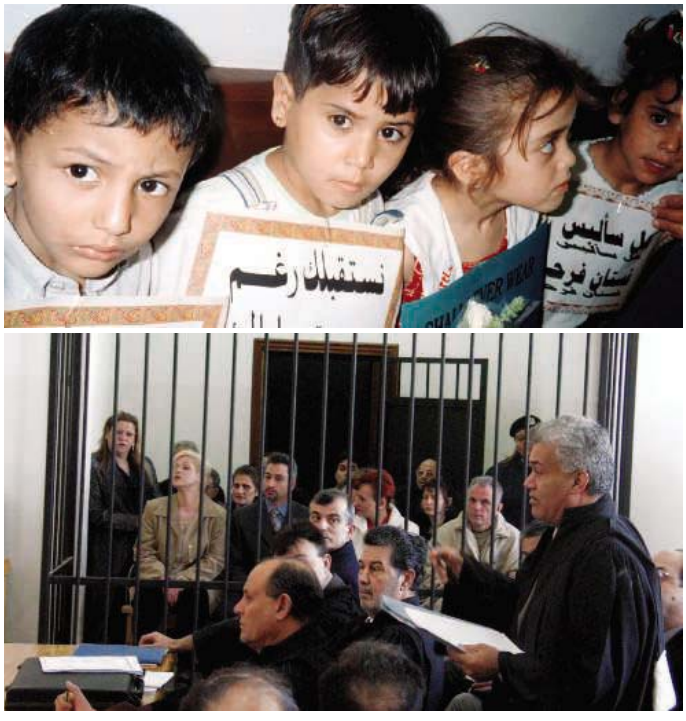
–DANIEL CLERY

CREDITS: GEORGI MILKOV

HUMAN RIGHTS

Scientists Urge Libya to Free Medics

U.S. scientists are adding their voices to mounting international pressure on Libya to release six foreign medical workers who could face execution within weeks. A letter published online this week by *Science*—written by virologist Robert Gallo, director of the Institute of Human Virology in Baltimore, Maryland, and co-discoverer of HIV, and signed by 43 other scientists—accuses the Libyan government of using the medics as scapegoats for the accidental infection with HIV of more than 400 children at a hospital in Benghazi. Libyan police rounded up the five Bulgarian nurses and a Palestinian doctor in 1999 and used torture to extract confessions that they had deliberately infected the children as an act of bioterrorism, according to human rights organizations. European scientists say poor hygiene likely caused the outbreak before the medics started working in the country (*Science*, 8 April 2005, p. 184).



Scapegoats. A Libyan judge sentenced six foreign medical workers (behind bars, *below*) to death, but scientists say they are innocent and that the Libyan children (*above*) were accidentally infected with HIV before the medics arrived.

The scientific evidence supported the medics' innocence, says Vittorio Colizzi, a virologist at the University of Rome "Tor Vergata" and an expert witness in the case. But it was disregarded by a Benghazi judge in 2004 in favor of damning testimony by Libyan doctors that was "full of errors and misunderstandings of basic molecular biology." The judge sentenced the medics to death by firing squad. The medics' final appeal is now being heard by the Libyan supreme court in Tripoli. Yet more scientific evidence has accumulated since then, says Colizzi, but the supreme court denied the defense an opportunity to present it. The final session is scheduled for 31 October; a verdict is expected soon after.

"We want to get people angry and influence their governments to do something," says Gallo. Libya's actions "send a chilling message" to international health workers that could discourage them from working in the developing world, says Gallo, adding that the Libyans themselves "need all the scientific help they can get to prevent another outbreak." For its part, the Libyan government has said that the case could be settled if Western governments pay "blood money" to satisfy the families of the infected children; a sum of $5.7 billion has been suggested.

Outrage among scientists has been building in recent weeks in parallel with diplomatic pressure from the U.S. and European governments. The U.K.'s Royal Society, the New York Academy of Sciences, and the Federation of the European Academies of Medicine, among others, have published open letters to the Libyan government calling for the medics' release. The Web site of AAAS (publisher of *Science*) contains directions for how individual scientists can add to the pressure.*

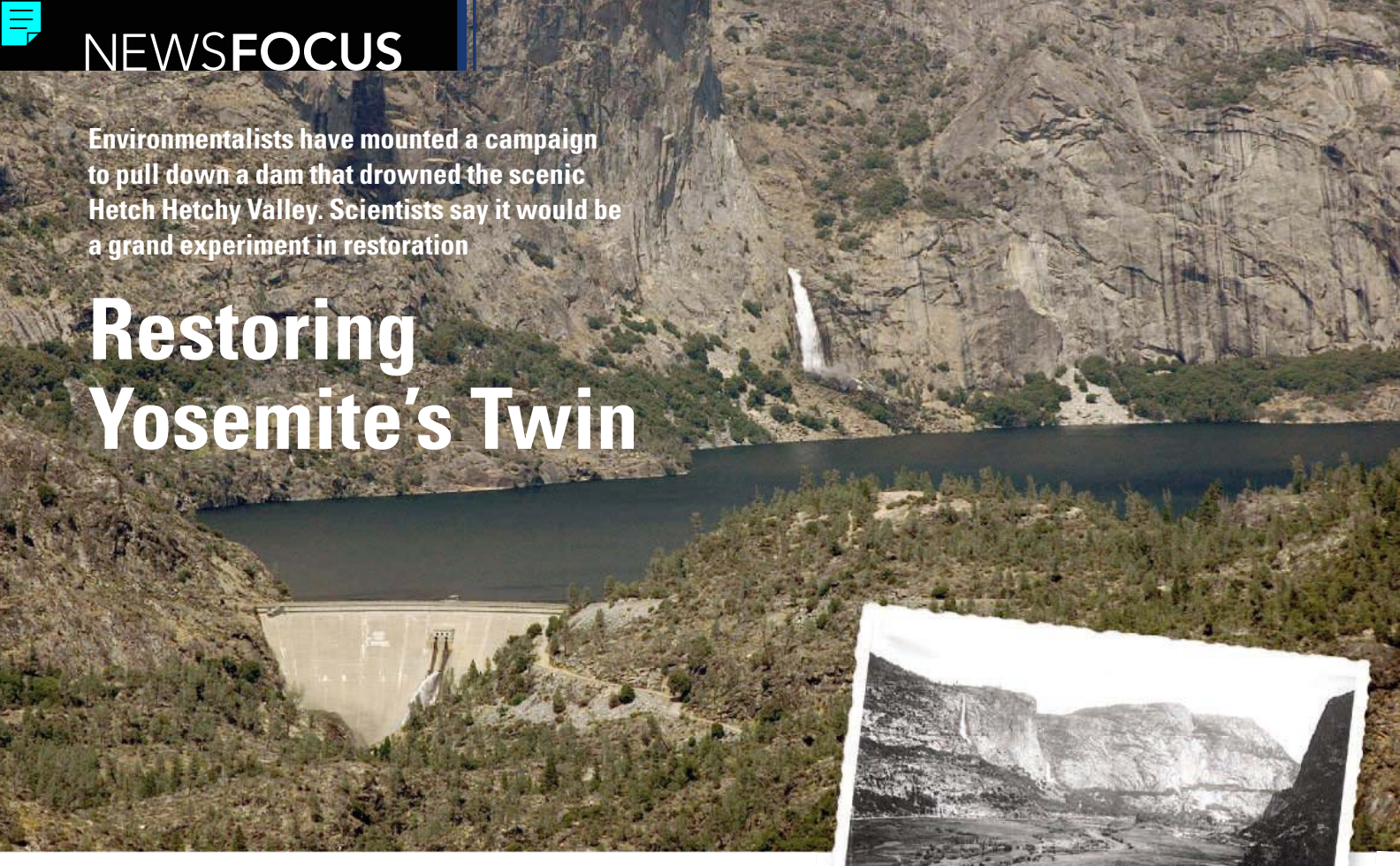
If the medics are not given a reprieve, says Gallo, "I will do everything I possibly can, starting with a call for an emergency session of the [U.S.] Academies of Science" to consider a "full scientific embargo." And if Libya decides to free the medics, Gallo says international praise and support should be equally swift: "They need to know that this virus is a problem for all of us, and we scientists can help."

–JOHN BOHANNON

* shr.aaas.org/aaashran/alert.php?a_id=328

Environmentalists have mounted a campaign to pull down a dam that drowned the scenic Hetch Hetchy Valley. Scientists say it would be a grand experiment in restoration

Restoring Yosemite's Twin



"It is a wonderfully exact counterpart of the Merced Yosemite, not only in its sublime rocks and waterfalls but in the gardens, groves and meadows of its flowery park-like floor."
—John Muir

JOHN MUIR SUFFERED HIS GREATEST defeat in 1913, when President Woodrow Wilson signed a bill authorizing the building of a dam in the naturalist's beloved Yosemite National Park. Muir had fought the proposal for a decade, but he and his supporters proved no match for San Francisco's growing thirst. The 100-meter-tall O'Shaughnessy Dam provided the city with a reliable, gravity-fed supply of water so clean that it still needs no filtration. The environmental cost was steep, however: The dam flooded Hetch Hetchy Valley, famed for its striking granite cliffs and waterfalls that rivaled its twin, Yosemite Valley, for grandeur.

Ever since, environmentalists have dreamed of undoing what they see as one of the greatest environmental sacrileges of the past century. Tearing down the dam and restoring the valley would "inspire people to replicate that restoration across the state, throughout the country, and around the world," says Spreck Rosekrans, an analyst at Environmental Defense in Oakland, California. Scientists view it as an unprecedented chance to study the ecological benefits of dam removal. "It's a huge opportunity to advance restoration science," says David Hart, an environmental scientist at the University of Maine, Orono.

It would also be a mammoth undertaking. No dam this size has ever been removed—the tallest is 20 meters. "The scale is fundamentally different," says Emily Stanley of the University of Wisconsin, Madison, who has studied smaller dams. With more than 500,000 cubic meters of concrete to demolish and truck out, and 825 hectares of valley floor that will emerge from the receding water like a moonscape, advocates and skeptics agree that the idea is uncharted territory.

Combine those uncertainties with the huge economic cost and California's legendary water politics, and it's clearly an uphill battle. But advocates say the proposal is gathering steam, and it did get a boost this summer when a state analysis concluded that it was technically feasible. "It's such a grand idea, an extraordinary idea, that it merits further study," said state assemblywoman Lois Wolk, who called for the report at a hearing in Sacramento this month.

Dam in the valley

This isn't the first time that someone has proposed restoring Hetch Hetchy. In 1987, an unlikely advocate emerged: Don Hodel, secretary of the interior during the Reagan Administration. During a visit to Yosemite National Park, he heard complaints about the crowding in Yosemite Valley and was floored to learn that a similar valley, Hetch Hetchy, had been turned into a reservoir. He has been championing its restoration ever since. "The U.S. pushes countries to develop national parks around the world, and we've got a dam in a national park. It's absolutely ridiculous," says Hodel, who now runs an energy consulting firm in Colorado.

But Hodel's attempt in the 1980s didn't go far. "I spoke with [Diane] Feinstein"—then mayor of San Francisco—"and she went ballistic," says Hodel. According to Hodel, Feinstein persuaded Congress to put language in the Interior appropriations bill that prohibited the agency from spending any money to further examine the idea. "We were totally stymied," Hodel says.

CREDITS: TIM CONNOR; (INSET) COURTESY OF THE NATIONAL PARK SERVICE/YOSEMITE MUSEUM

The way back. Historic photos could provide a guide to restoring the valley.

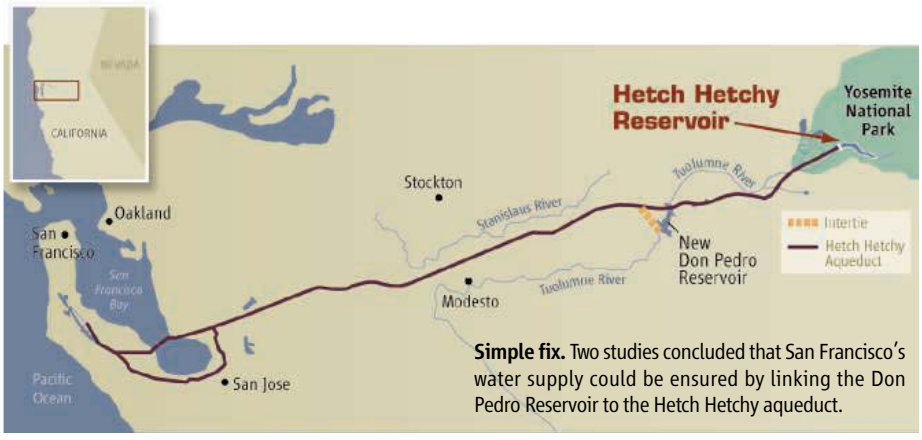
Feinstein maintained that Hetch Hetchy provides irreplaceable water storage for the city and keeps costs down. And the dam continues to generate 400 megawatts of green hydropower—now worth about $50 million a year. The state is not keen to lose those benefits. "San Francisco and the Bay Area are very concerned about these proposals," testified Michael Carlin, assistant general manager for water for the San Francisco Public Utilities Commission at the state hearing this month.

After Hodel's initial attempts were squashed, the proposal dropped off the radar screen for about a decade. It began to resurface in 1999, when environmental activist Ron Good and others founded Restore Hetch Hetchy, a small advocacy group in Sonora, California. Not long after, legendary environmentalist David Brower helped enlist the support of Environmental Defense, which has made the proposal a high priority.

The first feasibility issue was water storage: Could San Francisco get by without the dam? Environmental Defense's Rosekrans tackled the question using a computer model, concluding in a 2004 report that "a few straightforward plumbing fixes" could solve the storage issue, he says. His solution was to connect the Hetch Hetchy aqueduct—which takes water to San Francisco—to Don Pedro Reservoir, 56 kilometers downriver from the Hetch Hetchy Dam (see map); this would provide storage for more than the annual flow of the river.

Jay Lund, a civil engineer at the University of California (UC), Davis, has independently hit on the same engineering fix. "It provides unusually reliable storage relative to demand," Lund says. "There's still a lot of reliability even if you get rid of Hetch Hetchy." And that will remain true despite projected population growth and climate change, he and grad student Sarah Null show in a paper in the *Journal of the American Water Resources Association* published in April.

Although these findings are accepted by the scientific community, they "poke common wisdom in the eye," says fluvial geomorphologist Jeffrey Mount of UC Davis, so politicians remain wary. Everyone does agree that the costs of this replumbing and dam removal would be huge. Estimates vary from $1 billion over several years from Restore Hetch Hetchy to $3 billion to $10 billion from the state's Department of Water Resources. That's a bundle for a state that's already spent nearly $2 billion trying to fix its bay delta, for example.



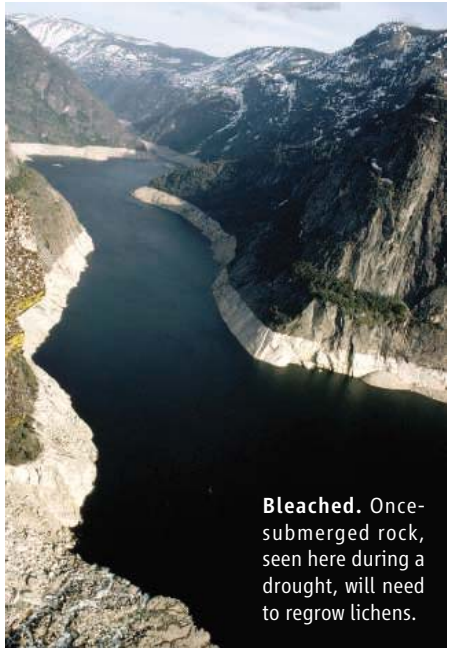
Simple fix. Two studies concluded that San Francisco's water supply could be ensured by linking the Don Pedro Reservoir to the Hetch Hetchy aqueduct.

Hodel thinks up to $1 billion could be saved by draining the water but leaving the dam in place; the concrete hulk would be a memorial to errant ways of the past. "People would find it fascinating to look at the dam, and they would say: 'Can you believe they put a dam in this beautiful valley?' "

At any rate, advocates for restoring Hetch Hetchy say the state shouldn't have to foot the entire bill, as the reclaimed valley would be national treasure. "All Americans have a stake in the outcome of the discussion," Good says.

A blank slate

But transforming the existing reservoir into the beautiful valley Hodel and others envision will not be easy. The goal is to restore 825 hectares that are now underwater with an array of habitats—wetlands, grasslands, oak savanna, and pine forest—essentially from a blank slate, says restoration ecologist Mark Cederborg of Hanford Applied Restoration and Conservation in Sonoma, who consults for Restore Hetch Hetchy.



Bleached. Once-submerged rock, seen here during a drought, will need to regrow lichens.

Figuring out exactly what to do will require some detective work. The reference, Yosemite Valley, has been heavily altered by invasive species, fire suppression, and other changes, so researchers will have to pore over historic photographs to help envision the predam landscape. Logistics will likely be difficult, too. The valley doesn't have roads and is surrounded by designated wilderness area, so workers may not be able to use heavy mechanical equipment. Herbicides use could be ruled out as well, because the river water will still be headed for city faucets.

The best approach would be to slowly lower the reservoir and restore the emerging land in stages over a number of years, says Joy Zedler, a wetlands ecologist at the University of Wisconsin, Madison, who in 2004 created an adaptive restoration plan for the valley with her graduate students. Zedler maintains that such a phased approach would enable researchers to study how well restoration techniques were working and modify them before the next stage. "You'd be wiser before you exposed more of the bottom," Zedler says. It would also spread out and lower costs, by improving techniques, and be easier on existing wildlife, she says.

This strategy, for instance, would reveal early on which invasive species are likely to be a problem—more than 140 thrive in Yosemite National Park—without letting them run wild over the whole valley. Invasives are a concern because the exposed terrain would be "like a vacant lot for plants to colonize," says Hart. Unlike most other restoration projects, this one would have a failsafe mechanism to deal with runaway invasives, Zedler adds: raise the water level and drown them.

Restoring the lichens that once gave the rock its distinctive color will be especially daunting. Because the lichens died when they were submerged, the exposed rock will appear bleached—a 100-meter-tall "bathtub ring"—

CREDITS (TOP TO BOTTOM): ADAPTED FROM THE HETCH HETCHY RESTORATION STUDY, THE RESOURCES AGENCY, STATE OF CALIFORNIA, 2006; GALEN ROWELL/CORBIS

Big Dams Ready for Teardown

As advocates push for the removal of O'Shaughnessy Dam in Yosemite National Park (see main text), they'll be closely watching a $185 million restoration project in Olympic National Park in Washington state. There, two dams on the Elwha River are slated to be demolished starting in 2009. "If it works well, it will open the door to removing large dams like Hetch Hetchy," says Emily Stanley of the University of Wisconsin, Madison. "I see it as the test case for very large dam removal."

The Elwha once boasted an estimated 400,000 spawning sockeye salmon and other fishes. But the Elwha Dam and Glines Canyon Dam, which were built in 1913 and 1927, respectively, to provide hydropower for a mill in the town of Port Angeles, cut off 112 kilometers of spawning runs and degraded the quality of the remaining 8 kilometers.

It took decades of legal wrangling to get a green light for the dams' removal. In 2000, after the Elwha Klallam Tribe and various environmental groups prevailed, Congress appropriated $29.5 million for the Department of the Interior to buy the dams. In an effort to restore the salmon runs, Congress has so far approved $17 million of $48 million for tearing down the dams and replanting the river valley. (The $185 million price tag also includes $75 million to provide a water-treatment facility, flood protection, and a sewer system for downstream communities.)

Removing the dams should take 3 years. A draft plan calls for draining the lake and blasting the Elwha Dam apart. The taller Glines Canyon Dam will be cut into 22-ton blocks and trucked away. Once the river runs free, it will wash away an estimated 40% of the 14 million cubic meters of sediment trapped behind the dams—far more than has ever been released from a dam before. "This would be an extreme case, but we don't anticipate any problems" for wildlife, says project manager and fisheries biologist Brian Winter of Olympic National Park. (Sediment likely won't be an issue at Hetch Hetchy; only a few centimeters are thought to have accumulated behind O'Shaughnessy, because the granite watershed erodes slowly.)

Cross section. O'Shaughnessy Dam in Hetch Hetchy Valley holds more water and has more concrete than the two Elwha River dams, but it has trapped less sediment.

Scientists would like to study the effects of sediment release on the Elwha, but there are no funds for research in the restoration budget. "We're trying to document the baseline conditions," says Jerry Freilich, research coordinator for Olympic National Park. Local universities have received a $1 million National Science Foundation grant to coordinate research efforts, but obtaining overall funding has been tough, Freilich says.

The sediment that remains in the valley will appear like natural river terraces, Winter says. Some 227 hectares of forest will be restored by planting native seeds and trees of various ages; the idea is to quickly create a diverse ecosystem in the hope of keeping invasive species from gaining a foothold.

Scientists say the salmon stand a good chance of recovery. Once the dams are removed, they will face few threats because most of the watershed is protected within Olympic National Park. **–E.S.**

after the water is lowered. A 1988 Park Service report estimated that it would take 80 to 120 years for the lichens to grow back on their own. Zedler proposes experiments to speed the recovery by propagating native lichens and testing various agents to help them adhere when sprayed onto barren rock.

Even with such experiments, no one can say for sure how the ecosystem is likely to respond. "If people think it will be pristine, they may be surprised," Stanley says. "It may end up creating a novel ecosystem that we haven't seen before."

Weighing priorities

The Hetch Hetchy experiment is not likely to happen anytime soon, even advocates concede. Only a few members of the state legislature are gingerly probing the issue, and opposition from Feinstein, who is now a U.S. senator, could hinder federal participation. "Politically right now, I don't see the stars aligned," says Mount.

The key reason: "The level of distrust among the various actors is very, very high," Dean Misczynski, director of the California Research Bureau, testified at the Sacramento hearing. The bureau has recommended appointing a blue-ribbon panel, with advisory groups of stakeholders and technical experts, to lay out ways to keep all the current beneficiaries of the dam from feeling they are getting a raw deal.

Aerial approach. Working without roads, crews may have to plant seeds and control erosion via helicopters.

Hodel remains upbeat about the long view. "It is inevitable that the dam will be removed," he says, adding that the biggest opposition to the project now is economic, not technical. "It's only a matter of time and negotiations."

But others point out that there are more pressing ecological needs. The habitat in Yosemite National Park is less endangered than other places, like southern California, where nature is being boxed in by development. Margaret Palmer of the University of Maryland, College Park, questions the wisdom of investing huge sums in fixing a short stretch of river in a relatively unblemished watershed. "The priority needs to be cleaning up our damaged streams, many in urban and agricultural areas," she says.

Still, many acknowledge the validity of the central argument. "That land was set aside for the purpose of preserving it as wilderness," says civil engineer William Graf of the University of South Carolina, Columbia, who studies dam removal. "We have not carried through on the promise." Muir, who died a year after Wilson approved the dam, would heartily agree.

–ERIK STOKSTAD

CREDITS (TOP TO BOTTOM): ADAPTED FROM THE HETCH HETCHY RESTORATION STUDY, THE RESOURCES AGENCY, STATE OF CALIFORNIA, 2006; ERICKSON AIR-CRANE PHOTO

GENETICS

Unraveling Pain's DNA

The genetics of pain, long overlooked, is now getting attention—but identifying the genes at work isn't an easy task

Neuroscientist Marshall Devor used to judge the aftermath of amputations much like everyone else. Some who have lost an arm or leg perceive a searing pain in the limb that's no longer there, whereas others are untroubled. The going theory was that this so-called phantom pain is psychological: "Some people can accept the loss of the limb, and some can't and spend their lives mourning," says Devor, who works at The Hebrew University in Jerusalem, Israel.

Then, about 2 decades ago, Devor's perspective shifted. He found that the offspring of rats who reacted strongly to a nerve injury in their leg, scratching and nibbling at their toes as if they were in pain, responded to weak stimuli with distress, unlike those born to rats less troubled by the same nerve injury. That research, published in 1990, was among the first to suggest that pain sensitivity has a genetic component.

Pinpointing the genes that predispose to pain, particularly chronic forms caused by nerve injuries, could help guide development of new pain treatments and even prevention. Such clues are desperately needed. Roughly 50 million adults in the United States suffer from persistent pain; it accounts for more than 20% of doctor's visits and 10% of health care dollars. "The solutions offered to patients are not satisfactory, and those that are cost dearly in terms of side effects," says Ze'ev Seltzer, a pain researcher at the University of Toronto in Canada.

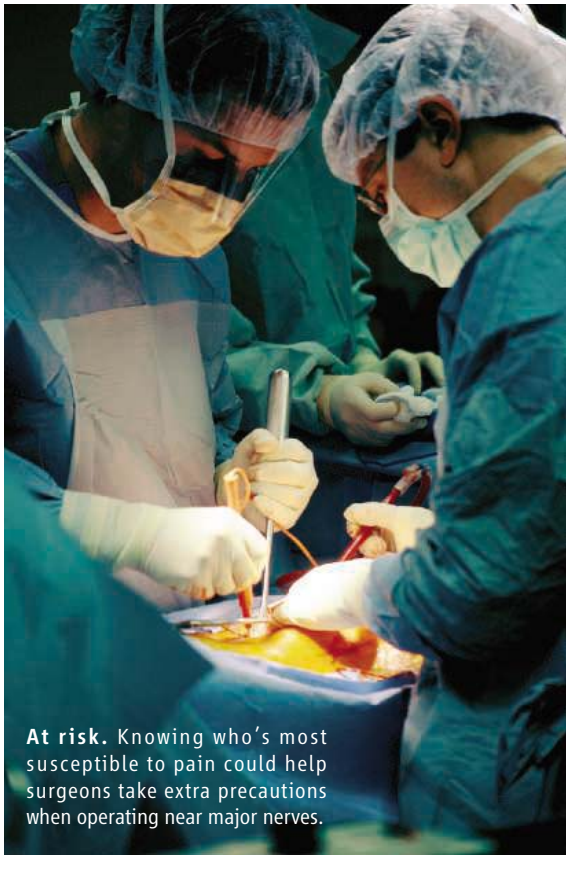
But perhaps more than other complex diseases spurred by a mix of problem genes and environmental insults, the pain field has faced an uphill battle in finding relevant genes. The role of a gene identified several years ago as an important key to pain sensitivity is now being questioned, for example. "Even 5 years ago, people really doubted that pain was genetic at all," says Luda Diatchenko, a geneticist at the University of North Carolina, Chapel Hill (UNC-CH), who is exploring the roles of genes in facial pain.

Still, a shortlist of so-called pain genes is emerging, and with a report in *Nature Medicine* this week, scientists tentatively added another. That gene, *GCH1*, is the first to be linked to neuropathic pain, a common, difficult-to-treat chronic condition caused by nerve damage that affects more than 2 million people in the United States.

A genetic thicket

Without an objective means of measuring pain, and with chronic pain patients exhibiting enormous variability in symptoms, designing human studies that produce lasting results has been challenging. And with hundreds of genes apparently influenced by pain in animal research, knowing which ones to pursue, and how influential they really are, is daunting, say researchers.

> "Even 5 years ago, **people really doubted that pain was genetic at all.**"
>
> —Luda Diatchenko, University of North Carolina, Chapel Hill



At risk. Knowing who's most susceptible to pain could help surgeons take extra precautions when operating near major nerves.

CREDIT: ROYALTY-FREE/CORBIS

To find *GCH1*, a team led by pain researcher Clifford Woolf at Massachusetts General Hospital in Boston started with what Woolf calls "a fishing expedition." They began by damaging nerves in rats and assessing how gene expression changed with the injury. The number of genes in nerve cells whose activity shifted was overwhelming—about 1500 in all. To pinpoint those that affected pain sensitivity rather than ones simply reacting to an insult, the researchers looked for altered expression that persisted for 6 weeks following nerve injury. That shrank the number of genes about 10-fold, to roughly 150. That was "still too many to deal with one at a time," says Woolf, so the team examined whether any of those genes were known to work together in a common pathway. That highlighted a trio of genes.

Then Woolf's group turned to Mitchell Max of the National Institute of Dental and Craniofacial Research (NIDCR) in Bethesda, Maryland, who has studied pain genetics in people, including a cohort of 147 people who were followed for 2 years after back surgery to relieve leg pain from a herniated disc. The researchers asked the volunteers to rate their pain every 3 months and also examined their DNA to see whether variations in any of the three genes correlated with the pain ratings. Two showed no effect.

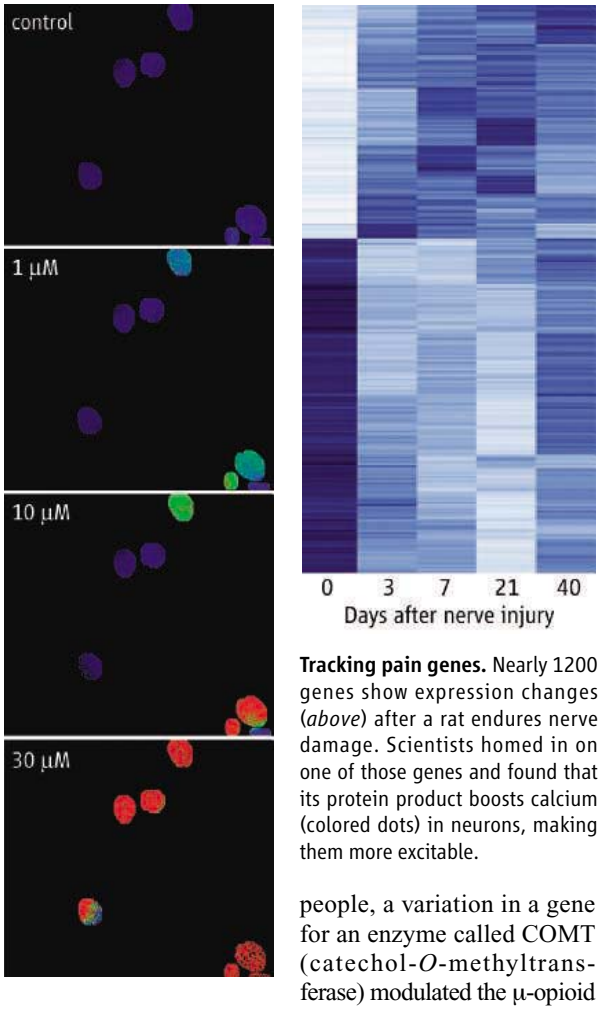
But a version of *GCH1* identified by a combination of 15 single-nucleotide polymorphisms (SNPs) was associated with less neuropathic leg pain in the first 2 years after surgery. People with two copies of that gene variant rated their pain as 0.06 on average, whereas those with no copies rated their pain 0.8 (Those with one copy rated their pain 0.44). *GCH1* controls production of a chemical called BH4, and Woolf's team found that administering it to rodents made sensory neurons more excitable.

It's not clear yet whether the *GCH1* connection will hold up in larger cohorts and those encompassing different types of pain. Still, the genes that have pain researchers most intrigued are those, like *GCH1*, that appear to influence the excitability of neurons. Although some studies, such as the one on facial pain in which Diatchenko is participating, focus on common chronic pain syndromes, other researchers are hoping that inherited pain disorders may be easier to dissect geneti-

cally and shed light on pain in general. At the Society for Neuroscience meeting in Atlanta, Georgia, last week, Stephen Waxman, a neurologist at Yale University, detailed the genetic mutations his group has found in a rare familial neuropathic pain syndrome called erythromelalgia. The people affected experience excruciating pain in their hands and feet when exposed to slight warmth, and abnormal vasculature turns their limbs bright red.

The mutations alter the gene for a sodium channel, a type of molecular gate that controls neural signaling. When this sodium channel has one of the mutations seen in erythromelalgia, it causes sensory neurons to fire with little provocation. "They scream when they should be whispering," says Waxman. And whereas sodium-channel mutations have not been linked to more prevalent kinds of chronic pain, Waxman's group and some British scientists have found that the channel appears to play a role in inflammatory pain in animals. "We're beginning to ask the question, 'Are there polymorphisms [in this gene] … that don't cause disease but are associated with high or low thresholds of pain?' " says Waxman.

Increasingly, scientists believe that a person's pain thresholds reflect their risk of developing chronic pain. After all, only 5% to 15% of people wounded in car accidents or by gunshots, or suffering from shingles, will develop chronic neuropathic pain—perhaps because they possess a combination of genetic mutations that increases their sensitivity to pain.



Tracking pain genes. Nearly 1200 genes show expression changes (*above*) after a rat endures nerve damage. Scientists homed in on one of those genes and found that its protein product boosts calcium (colored dots) in neurons, making them more excitable.

The face of pain

As the *GCH1* story shows, finding gene variants behind pain is a complex task. The tool typically employed to tease out the genetic component of other complex diseases—twin studies—is nearly impossible to use in chronic pain because few twins will suffer the same environmental insult that leads to pain. "Chronic pain is probably the classic example of gene-environment interaction," says Jeffrey Mogil, a neurogeneticist at McGill University in Montreal, Canada.

Another challenge in pain genetics is knowing whom to study. For example, in 2003, researchers led by Jon-Kar Zubieta of the University of Michigan, Ann Arbor, and David Goldman of the National Institute on Alcohol Abuse and Alcoholism in Bethesda, Maryland, reported in *Science* that among people, a variation in a gene for an enzyme called COMT (catechol-*O*-methyltransferase) modulated the μ-opioid system (21 February 2003, p. 1240). That system naturally helps the body control pain. The find initially electrified the research community, because it suggested that the gene influences a person's pain sensitivity.

But efforts to confirm a broad role for the gene in pain have faltered. One possible explanation, says Woolf, is that various research teams have focused on different "phenotypes": individuals with different types of pain. A study led by Raymond Dionne of NIDCR reported this summer that the gene for COMT played little role in pain sensitivity following wisdom tooth surgery. The original *Science* study, on the other hand, exposed 29 healthy volunteers to painful injections in jaw muscles. That sample size is small, note researchers, and it's still not clear how much overlap exists between genes that govern experimental pain and those guiding chronic pain sensitivity or susceptibility.

Most pain researchers, however, still believe that COMT has a role to play. Last year, Diatchenko and her colleagues found that different combinations of four SNPs in *COMT* affected the risk of developing a form of musculoskeletal facial pain known as temporomandibular joint disorder. Those with one particular combination of SNPs were less than half as likely to suffer from the disease and were much more resistant to pain. "The [COMT] story is probably a lot more complicated than we thought," says Mogil.

Indeed, Mogil has found in mice that the genes governing hypersensitivity to touch are generally not the same as those influencing hypersensitivity to cold, or to heat. "Our animal studies show very clearly that all these symptoms dissociate from each other," he says, suggesting that in different pain phenotypes, the genetic combinations at work vary.

In humans, however, various types of pain are often lumped together, and it's virtually impossible to distinguish between the physical pain cause by overly excited sensory neurons and the patient's emotional response to pain. Both, says Diatchenko, feed into an individual's perception of his or her pain.

Diatchenko hopes that the facial pain study she's involved in, which is led by her colleague William Maixner of UNC-CH, may provide a framework for teasing apart genetic and environmental drivers of chronic pain. The study, which garnered $19 million from the National Institutes of Health—a remarkable figure, given that only 1% of the agency's $28 billion budget goes to pain research—will follow 3200 healthy individuals and 200 who have facial pain. Roughly 5% to 15% of the healthy group is expected to spontaneously develop facial pain as well. The researchers will hunt for both environmental factors and genetic candidates that appear to increase an individual's susceptibility to such facial pain and other pain conditions.

"The main question is, 'Can we predict the people who are predisposed to chronic pain conditions?' " both facial pain and beyond, says Diatchenko. Such a skill could allow physicians to take extra care in potentially dicey scenarios—such as offering additional protection to nerves at risk during surgery. Given the complexity and the halting pace of pain genetics research so far, that would be a giant step forward.

–JENNIFER COUZIN

CREDITS (LEFT TO RIGHT): A. BINSHTOCK; R. GRIFFIN AND M. COSTIGAN

PROFILE: DIOLA BAGAYOKO

Failure Is Not an Option for These Minority Students

Southern University physicist Diola Bagayoko uses tough love to expand and diversify the pool of scientific talent

Sharon Daniels was a physics major at Southern University (SUBR) in her hometown of Baton Rouge, Louisiana, when she got married, had a baby, and dropped out of college. When the marriage went sour, she took a job in Houston, Texas. But 2 years later she was back in Baton Rouge, where she learned that her former professor, Diola Bagayoko, wanted to see her.

When Daniels showed up at his office, Bagayoko gave her a scolding. "If you're thinking you'll take care of your kid right now and finish your degree later, you are putting yourself in quicksand," Bagayoko told her. He asked Daniels to think about her high school friends, few of whom were doing well. Then he turned on the charm. "You have the talent and the intellect needed to do this," he said. Her 3.0-plus grade point average made her a good candidate for financial aid, he added, and her coursework was recent enough that it would still count toward her degree.

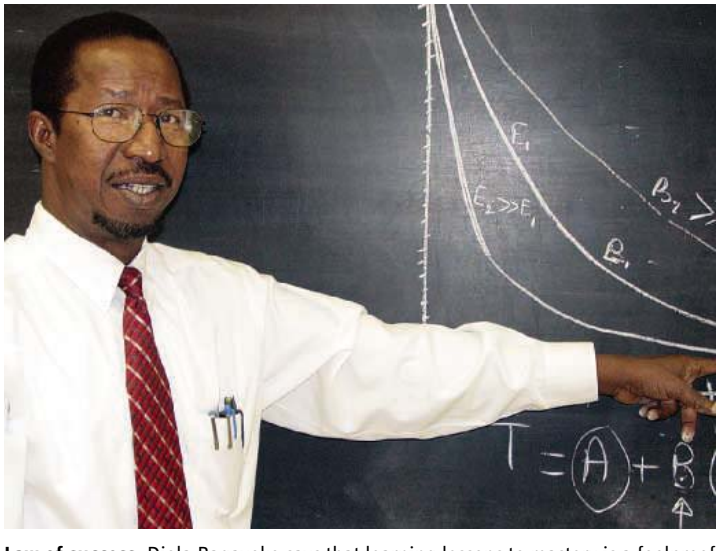
The sales pitch worked, and in 1992 Daniels graduated and began a career as a software programmer and technical writer. For 2 decades, Bagayoko has helped African-American students like Daniels earn science and engineering degrees from SUBR, a historically black institution where a significant percentage of students are the first in their family to attend college. And he continues to mentor them through graduate programs around the country and into scientific careers. His efforts have earned him two presidential mentoring awards and persuaded his university, a predominantly undergraduate institution, to make mentoring a factor in its tenure and promotion process.

Bagayoko, who grew up in Mali and came to the United States for graduate school, has done much of this work through the Timbuktu Academy, a program he started in 1990 with funding from the National Science Foundation (NSF) and the Defense Department's Office of Naval Research. Named after the West African university that stood on the banks of the Niger River from the 12th to the 16th centuries, the academy conducts intensive summer camps for middle and high school students to prepare them for science and engineering majors in college. It also shepherds a handful of students through undergraduate science and engineering programs at SUBR by providing them with academic advice, extra tutoring, and a solid research experience outside the classroom. Although the program is open to any student, nearly all of the applicants are from racial and ethnic groups traditionally underrepresented in science, and the majority are African-American.

Bagayoko, 57, is proud of his record. Of the 600 high school students who have attended the academy's summer programs, 80% have gone on to major in STEM (science, technology, engineering, and mathematics) disciplines at colleges around the country. Of the 150 students who have earned their bachelor's degree from SUBR with support from the academy, more than 60% have pursued advanced degrees in scientific disciplines.

Although comparisons are difficult because of the paucity of good longitudinal data, the program is one of the most effective pipelines for channeling African Americans into science and engineering careers, says Anthony Junior, manager of the Department of Navy's Historically Black Colleges and Universities program, which has funded the academy at $600,000 a year since 1993. Bagayoko's own department has reaped the rewards: On a campus that loses half of its freshman class, 90% of first-year students who choose to major in physics—nearly all of them academy scholars—earn a degree in 4 years.

Since 1995, Bagayoko has replicated the academy's mentoring model across 10 other Louisiana institutions with a grant from NSF's Louis Stokes Alliance for Minority Participation (LSAMP) program. Funding officials and colleagues familiar with Bagayoko's work say he succeeds by using time-tested ingredients for good mentoring—building students' self-confidence, involving them in research, and monitoring



Law of success. Diola Bagayoko says that learning lessons to mastery is a foolproof road to success for students.

CREDITS (TOP TO BOTTOM): MONIKA WRIGHT; Y. BHATTACHARJEE/*SCIENCE*

them closely—and adding in his unique blend of kindness and charisma. "Most of these practices are laid out in the literature," says A. James Hicks, NSF's program director for LSAMP. "But it takes special individuals like Diola Bagayoko to implement them."

Paying forward

Bagayoko's ever-present suit and tie belie his youthful exuberance. He uses an expressive face and a deep, distinctive voice to great effect in the classroom. There's a strong hint of French colonial Africa in his speech, which he salts with vigorous gestures. Peering over his glasses to gauge his listener's reaction, he laughs loudly and slaps his knee after making a point. Students stream in and out of his office for help with assignments, which he crams into a punishing schedule that stretches into the evening and includes weekends.

Bagayoko traces the origins of his passion to help the underserved to his teachers in Bamako, Mali's capital. One helped him skirt an age limit for entering secondary school, and another expanded his horizons with a collection of books by Victor Hugo. "The only way I could thank him was by reading them backward and forward. My capacity in French ballooned as a result," he says.

After getting a bachelor's degree in physics and chemistry in Mali, Bagayoko came to the United States to study solid state physics at Lehigh University in Bethlehem, Pennsylvania. Moving to Louisiana State University in Baton Rouge for his Ph.D., Bagayoko recalls how his dissertation adviser arranged with the school chancellor to keep the university's computing center open during holidays so that Bagayoko could have uninterrupted access to the facility. In his first year, the adviser paid for him to attend an American Physical Society conference in Chicago, Illinois, even though he didn't have anything to present. "I vowed that I'd be back at next year's conference with a presentation of my own," he says. He kept the promise.

Bagayoko didn't forget those experiences when he joined the SUBR faculty in 1984. "I realized that I was the product of the good work of many people," he says. "I wanted to say thanks." At the urging of his chemist wife and fellow SUBR professor, Ella Kelley, he created a structured mentoring program based on the simple idea that an individual becomes more proficient at a task with practice.

The concept is embodied in a 1920s theory called the power law of human performance. Bagayoko uses it as a motivational tool in combination with the idea that most knowledge—particularly scientific knowledge—is acquired cumulatively. "The typical African-American student enters college with elements in his background that are unfavorable to learning—bad grammar, poor vocabulary, a poor grounding in basic math—none of which is his fault," he says. But if a professor is willing to fill those holes, "success is guaranteed."

Over the years, Bagayoko has wielded the power law like a machete to eradicate the self-doubt among many African-American students toward science. "I tell them that irrespective of what they may have heard before, there's a law out there that not only says they can do well in science but also describes how." The program also helps high school students improve their grammar and vocabulary skills, increasing their chances of attending a good college.

In mentoring undergraduates supported by the academy, Bagayoko puts great emphasis on research, both with professors on campus during the school year and in labs around the country during the summer. Students who have worked with him say he monitors their progress closely, using carrots such as a chance for extra coaching and sticks such as the threat of pulling their financial aid.

"He asks questions like: Why are you spending so much time with your sorority?" says Zelda Gills, one of his earlier students who is now a scientist at the U.S. Nuclear Regulatory Commission. "When he wants you to do something, he never says: 'Could you do this?' It's always: 'You will do this.' He can be very stern, but you know that it's for your own good."

Generation 2.0. Zephra Bell and her mother are both graduates of Bagayoko's Timbuktu Academy.

CREDIT: D. BAGAYOKO

Better things to do

The 34-year-old building where SUBR's physics department is located bears a tired look. Several lights in the hallways and bathrooms are burnt out, and some of the water fountains don't work. But neither the threadbare conditions nor the oppressive August heat stop Bagayoko from delivering his message to the incoming class of academy and LSAMP scholars.

His assistant distributes a handout describing the power law, his gospel. "One thing it tells you is that if you are studying a lesson and cannot understand it, it probably means there is some critical background material that you may not have," he booms. "Go see a faculty member to find out what it is."

The 1-hour lecture includes suggestions on how to behave outside the classroom, including avoiding fights. "I won't fight, not because I can't, but because I have sound judgment," he counsels them. "When I get into a situation like that, I say to myself, 'This person probably doesn't manipulate Maxwell's equations as well as I do. I have better things to do, like developing new theories or building new devices.' "

Bagayoko then rattles off the names of former academy members who, presumably, took his advice to heart. He mentions Anthony Pullen, an SUBR graduate now studying theoretical astrophysics at the California Institute of Technology in Pasadena. "A few years ago, these people were sitting in this auditorium, just like you," he says. "They delivered for themselves and their families. You can, too."

The students say they welcome the guidance. "Some of us here need to be told and retold that academic achievement is valuable," says Jonathan Dooley, a freshman who grew up in an impoverished Los Angeles, California, neighborhood. Dooley's African-American father left when he was very young, and his Hispanic mother told him in kindergarten that he would end up homeless if he didn't go to college. "Knowing that there are blacks and Hispanics out there with Ph.D.s in science means a lot to me," says Dooley.

Bagayoko's impact can extend far beyond a student's professional training. Two years ago Daniels, who has stayed in touch with Bagayoko, asked him to consider her daughter, Zephra Bell, whom she had home-schooled, for admission into the academy. He did, and Zephra made the cut: She is now 2 years away from earning a bachelor's degree in physics at SUBR. "I had no ideas about her going anywhere else," Daniels says. "She's in good hands."

–YUDHIJIT BHATTACHARJEE

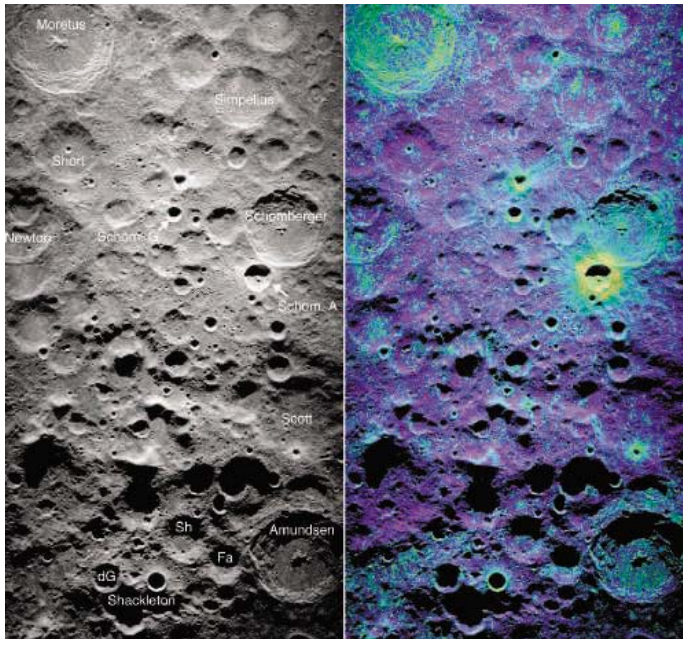
An Even Drier-Looking Moon

NASA would like nothing better than to find water on the moon. Astronauts could drink it as well as convert it to rocket fuel for their leap on to Mars. The agency's immediate plans for lunar exploration are largely geared to the search for lunar water ice, but two new studies have failed to find any sign of it, despite previous reports of ice deposits cached in the deep chill of permanent shadows. It appears that nothing short of a dedicated rover mission could settle the question.

At the meeting, a new analysis raised questions about signs of water returned by an orbiting spacecraft. Planetary scientist David Paige of the University of California, Los Angeles, and colleagues looked for places on the moon where the sun never shines—in the shadows of crater walls near the poles. Presumably, water delivered by impacting comets over the eons could have made its way to these cold traps and been preserved as ice just beneath the surface of the loose soil. Paige and his team calculated lunar temperatures across the surface and the subsurface, starting with the chilling effect of shadows and including heating by reflected sunlight and by adjacent sun-warmed rock.

There are indeed crater-hosted cold traps near the poles as cold as 50 kelvin, the group found. But earlier reported signs of ice do not necessarily coincide with the cold traps. Eight years ago, the orbiting Lunar Prospector measured neutron emissions from the moon induced by cosmic rays. It found what looked like deposits of hydrogen—presumably in the form of water ice—in the right general areas (*Science*, 13 March 1998, p. 1628), the polar regions, but mostly not where the calculated cold spots are. "We can probably say with some confidence that not all cold traps are filled with ice," Paige says.

Another new study questions the other sort of evidence for lunar ice. In the 19 October issue of *Nature*, planetary scientist Donald Campbell of Cornell University and colleagues report that the highest-resolution radar study yet of the moon's south polar region appears to rule out rich ice deposits there.



Not ice. A radar signal associated with ice (yellow-green, *right*) appears not only in shadowed Shackleton crater (*bottom*) but also in sunlit areas.

Radar signals bounced off the moon in 1996 by the orbiting Clementine spacecraft and received on Earth had hinted at massive ice deposits in craters near the moon's south pole.

When Campbell and his colleagues used two giant Earth-based radio dishes to bounce radar signals off the moon, they did find Clementine's telltale signal—an unusual effect on the reflected signal's polarization previously associated with ice. But, thanks to the 20-meter resolution, they could see that the polarization effect was usually in the wrong places. Although it appeared in the permanently shaded wall of Shackleton crater, for example, it also showed up in well-lit Schomberger crater and around many smaller young craters, all areas roughened by crater ejecta and slumping rock. "Right now, the explanation for the lunar [polarization effect] has something to do with reflection between rocks and boulders rather than ice at the poles," says planetary scientist Bruce Hapke of the University of Pittsburgh in Pennsylvania.

The new studies cast a shadow on NASA's next lunar mission: an ice-oriented scientific exploration of the moon meant to pave the way for humans' return. Most of the instruments on the Lunar Reconnaissance Orbiter (LRO), to be launched in October 2008, can measure properties relevant to lunar ice. And the piggyback experiment to LRO—a crash landing into a shadowed crater, intended to kick any ice there into view—is all about water. Not everyone is optimistic. "I don't think you can [prove the existence of ice] remotely," says planetary scientist William Feldman of the Planetary Science Institute in Tucson, Arizona; he headed the Lunar Prospector neutron investigation. "You have to go there in a rover. That's hard, especially if it's 80 K."

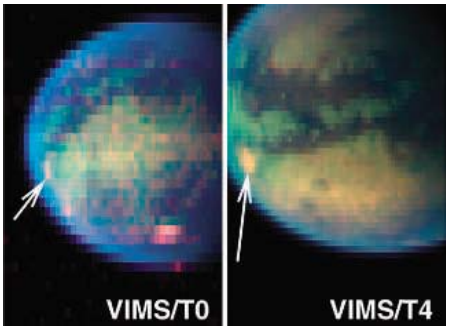
CREDIT: D. B. CAMPBELL *ET AL.*, *NATURE* 443 (19 OCTOBER 2006)

Titan Lives—Geologically, at Least

Saturn's largest moon, Titan, suffers under its heavy atmosphere, as the Cassini spacecraft and its Huygens lander quickly revealed after they arrived. Brooding clouds, icy terrains gouged by river-cut channels, lake-dotted high latitudes, and great dune fields attested to geologic activity imposed from above. And Titan had also driven surface changes from within itself, at least in the geologic past. Flows of icy "lava," which had obviously erupted from inside Titan, lace the landscape.

Now Cassini team members report the first detection of a change on the surface of Titan since Cassini's arrival, and it appears to be powered from within. "Once thought of as frozen in time, Titan should be added to the bodies with active volcanism," said Cassini team member Robert Nelson of the Jet Propulsion Laboratory in Pasadena, California.

Cassini's view of Titan's ongoing geologic activity remains fuzzy. On its first pass by the moon, in July 2004, members of the Visual and Infrared Mapping Spectrometer (VIMS) team noticed a bright spot in Titan's southern mid-latitudes. At 70,000 square kilometers, it was the brightest part of the moon. Then it got brighter. It doubled in brightness and in size by March of 2005 and then dimmed and shrank back to its original appearance by November of the same year, Nelson reported at the meeting. Then it went



Flare-up. Between Cassini visits, something came out of Titan to intensify its bright spot.

through the same cycle again by March of this year. "This is a major event," said Nelson. After comparing the spot with adjacent areas, he and VIMS team colleagues conclude it isn't a cloud or a fog bank. "We're fairly comfortable with the idea that change is happening" on the surface, he says.

"The observations are spectacular," says planetary physicist David Stevenson of the California Institute of Technology in Pasadena. The changes are generated from within, he agrees. "The question is, what is the actual process?" He feels "volcano" is too strong a word to use at this point, evoking as it does great gushings of magma. In the case of frigid, icy Titan, any gushings would likely be of a slushy water-ammonia mix. Stevenson, who did the early work on such chilly eruptions, leans toward some lower-energy process: something unlike anything on Earth, which could still alter an area the size of Ireland in a month or two. Suggestions are welcome.

The Kuiper Belt Loses Some of Its Mystery

For 200 years, scientists have believed that the solar system emerged from a swirling disk of gas and dust. But that doesn't begin to explain the myriad peculiarities of the solar system, so planetary dynamicists are striving for a "theory of everything": one all-encompassing scenario that will put each planet, asteroid, and icy leftover of solar system formation in its proper place. A recent contender—one in which the early solar system "goes crazy for a while"—got another test at the meeting.

About the most peculiar part of the solar system is the Kuiper belt, the disk of icy remnants beyond (and including) Pluto. Kuiper belt objects (KBOs) just haven't behaved the way leftovers from a simple disk should. For example, the outer edge of their disk ends abruptly at 50 times the Earth-sun distance, for no obvious reason. Some KBOs lead well-ordered lives in nearly circular orbits in the same plane as the planets, whereas others fly around in inclined, elongated orbits. The list goes on.

With so many quirks, the Kuiper belt seemed like a good test for a model of solar system evolution developed by dynamicist Alessandro Morbidelli of the Observatory of the Côte d'Azur in Nice, France, and three international colleagues. Their "Nice model" had already done a credible job of getting the four outer planets into slightly elongated and tilted orbits and raining debris into the inner solar system in the so-called late heavy bombardment (*Science*, 3 December 2004, p. 1676). The trick was to start the Nice model with the newborn outer planets closer in and more tightly bunched than they are at present. Then Saturn would drift outward until falling into a gravitational link with massive Jupiter. Jupiter could then pump orbital energy into Saturn, which in turn would stir the outermost solar system into a chaotic frenzy.

In their new modeling, Morbidelli and his colleagues followed the fate of lingering planetesimals flung outward by orbitally crazed Uranus and Neptune. In the end, "we succeed pretty well," says Morbidelli. The model's planetesimals end up more or less where the KBOs are today and usually in about the right amounts. They do that by filling the space made chaotic by the Jupiter-Saturn link and getting stranded there when Saturn breaks out of its jovian gravitational interaction. The outer edge of the disk is where the continuous orbital chaos ends, for example.

"They're putting together a nice story," says dynamicist Jack J. Lissauer of NASA's Ames Research Center in Mountain View, California. Nice but not perfect, he adds. For example, the Nice model—like all others—fails to produce enough KBOs in particularly elongated and inclined orbits. Dynamicist Renu Malhotra of the University of Arizona, Tucson, has a more fundamental reservation. "I'm not convinced their model's initial conditions are quite plausible," she says. She doesn't see how that many planetesimals could linger 700 million years until the late heavy bombardment. So she would like to see yet more KBO peculiarities tested.

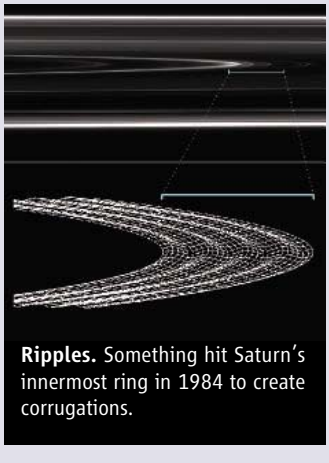
–RICHARD A. KERR

Snapshots From The Meeting >>

Breakups. Planetary bodies tend to run into each other in our crowded solar system. But three unrelated reports at the meeting brought home just how frequent—and recent—catastrophic collisions have been. Planetary astronomer Kristina Barkume and her colleagues at the California Institute of Technology in Pasadena reported the first discovery of a "family" of Kuiper belt objects beyond Pluto. The newly recognized family includes the 2000-kilometer-long "parent" 2003 EL61 and three 100-kilometer fragments, all following nearly identical orbits since EL61 suffered a catastrophic collision.

Closer to home, planetary scientist David Vokrouhlický and colleagues at the Southwest Research Institute in Boulder, Colorado, identified four new families in the asteroid belt that could be traced to collisions in the past 600,000 years, the most recent just 70,000 years ago. That raises the possibility that asteroidal dust from collisions might be preserved in Antarctic ice cores.

And planetary ring specialist Matthew Hedman of Cornell University and colleagues reported that a spiral ring of Saturn imaged in 1995 by the Hubble Space Telescope had tightened up by 2006 when the Cassini spacecraft imaged it. The spiral ring, they conclude, must actually be shadow-casting corrugations in the broader D ring, the corrugations having been formed by a recent impact. Quite recent, in fact: 1984.



Ripples. Something hit Saturn's innermost ring in 1984 to create corrugations.

Cataclysm confirmed. The humongous impact craters that create the "man in the moon" seem to have formed in one horrendous storm of giant impactors 700 million years after the solar system's formation. But that could be deceptive, some planetary scientists have argued. Those impacts may have been just the tail end of a dwindling rain of bodies left over from the rather messy birth of the solar system. Dynamicist William Bottke and colleagues at the Southwest Research Institute in Boulder, Colorado, decided to test the declining-bombardment scenario by simulating the fate of lingering planetesimals in a computer model. When they put in enough massive bodies to pummel the moon long after its formation, the bodies collided with one another and ground themselves down until they were too small to do the job. Whatever battered the moon, they conclude, it wasn't the tail end of solar system formation.

–R.A.K.

CREDITS (TOP TO BOTTOM): J. W. BARNES *ET AL.*, *SCIENCE* 310, 5745 (2005); NASA/JPL/SPACE SCIENCE INSTITUTE

EDITED BY YUDHIJIT BHATTACHARJEE

Two Cultures

ONE-WAY STREET. "I tried my damnedest to get out of doing this," grumbled noted architect Frank Gehry as he began his talk at this year's meeting of the Society for Neuroscience (SfN) held in Atlanta, Georgia, this month. By the end of the event, it wasn't clear whether the remark had been made in jest.

Gehry's lecture, the second installment in SfN's Dialogues between Neuroscience and Society series, described the creative process behind several of his landmark buildings. That was followed by an onstage conversation with Fred Gage, a neuroscientist at the Salk Institute in San Diego, California. Gage said scientists would like to investigate how built environments affect brain function and asked Gehry whether he would want to know what they find out. "No, I don't," he replied, explaining that such knowledge might impose unwanted rules on architects.

Although Gehry's appearance wasn't as controversial as last year's lecture by the Dalai Lama (*Science*, 18 November 2005, p. 1104), his talk elicited mixed reviews. Several neuroscientists said they had wanted to hear more about what brain researchers and architects might learn from each other. But others found plenty of food for thought. "I had several conversations with colleagues trying to muse about what kind of processing goes on within [his] brain," says SfN President David Van Essen of Washington University in St. Louis, Missouri. Next year's talk is by PalmPilot inventor Jeff Hawkins (*Science*, 6 October, p. 76).

MOVERS

BABY STEPS. The youngest institute among the National Institutes of Health has picked an NIH insider to lead its fledgling intramural research program.

As the first scientific director of the 6-year-old National Institute of Biomedical Imaging and Bioengineering (NIBIB), Richard Leapman will guide the expansion of what is currently a $4 million program to a proposed $8 million in 2007. "I hope we can have a big impact without having a big budget," he says, noting that the program will focus on nanomedicine and an ongoing initiative titled Imaging from Molecules to Cells.

The program will also assume some or all projects currently run by NIH's Division of Bioengineering and Physical Science, which Leapman has supervised since 1999 as acting director. NIBIB offers a much better fit for that portfolio, says Donna Dean, who served as the institute's temporary head before Roderic Pettigrew took over in 2002.

NEW *PNAS* EDITOR. Randy Schekman, a cell biologist at the University of California, Berkeley, is the new editor-in-chief of the *Proceedings of the National Academy of Sciences*. He replaces Nicholas Cozzarelli, who died of lymphoma in March after 12 years at the helm.

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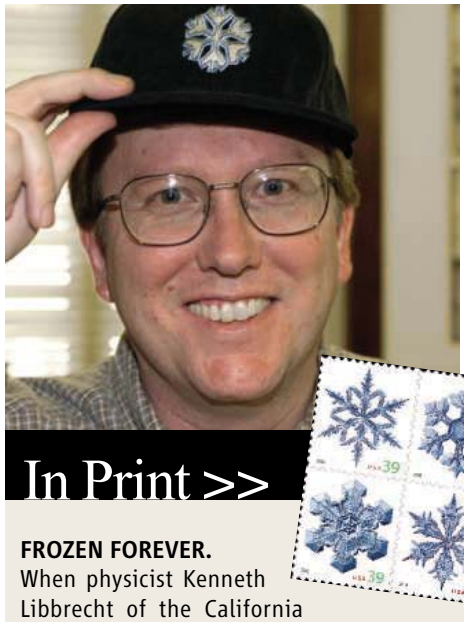
IN THE COURTS

IN LIMBO. Loling Song, a Chinese-born cell biologist at Harvard Medical School in Boston, has received a $750,000 grant from the U.S. National Cancer Institute. But she can't spend it because the award can only be made to U.S. citizens or permanent residents, and her application for the requisite green card, filed in April 2004, is still pending.

Faced with the prospect of losing the grant unless she gets resident status by 30 November, Song this month sued the Department of Homeland Security, which handles such applications, and the FBI, which does the required background checks. The suit, filed in U.S. District Court in Boston, charges that the government's delay is disrupting Song's "medical research on breast cancer, an issue of national interest."

"It's hard to believe that it takes the U.S. government 2 years to do a background check on an individual," says attorney Maureen O' Sullivan about her client, who is a Dutch citizen who came to the United States in 2004. FBI spokesperson Bill Carter says that 95% of security checks are done within a week but that some require communicating with other agencies as well as foreign governments. The government has 60 days to respond to the suit.



In Print >>

FROZEN FOREVER. When physicist Kenneth Libbrecht of the California Institute of Technology in Pasadena mails out Christmas cards this year, the envelope will also contain a personal touch: stamps bearing pictures of snowflakes that he took himself. Libbrecht, who studies ice-crystal formation, began photographing snowflakes 5 years ago, and in 2003 he co-authored *A Field Guide to Snowflakes*. It drew the attention of the U.S. Postal Service, which this month issued a set of four snowflake stamps, each with a face value of 39 cents. How many did Libbrecht buy? "A hundred or so," he says. "People seem to like them."

CREDITS (TOP TO BOTTOM): RIC FRANCIS/AP PHOTO; KENNETH LIBBRECHT; NIH

LETTERS

edited by Etta Kavanagh

Editorial Expression of Concern

IN THE 17 FEBRUARY 2006 ISSUE, WE PUBLISHED THE STUDY "*CDX2* GENE EXPRESSION AND trophectoderm lineage specification in mouse embryos" by K. Deb *et al.* (*1*). It has come to our attention, through communication with Robert Hall of the Provost's office at the University of Missouri Columbia and the senior author of the paper, R. Michael Roberts of the University of Missouri Columbia, that there is an ongoing investigation of this study by the University of Missouri. We are therefore informing readers that the results reported therein may not be reliable.

DONALD KENNEDY

Editor-in-Chief

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1. K. Deb, M. Sivaguru, H. Yul Yong, R. M. Roberts, *Science* **311**, 992 (2006).

On the Lack of Women in Academic Science

REFLECTING ON MY OWN EXPERIENCES IN the 1950s and 1960s with discrimination against the hiring of women in physics and the foolish and transparent excuses that were offered to me, the report of the U.S. National Academies of Science on the paucity of women scientists in academia ("Universities urged to improve hiring and advancement of women," A. Lawler, News of the Week, 22 Sept., p. 1712) is not new information. However, I was confident 40 years ago when I was offered the opportunity to start the physics department at George Mason University that talented women would apply for positions in our department. Women realized that the presence of a senior woman in a decision-making role signified that their application would be looked at equitably. This simple fact meant that we were always able to select good faculty from both genders. We never set out to specifically hire women. It was self-fulfilling. During these 40 years, seven men and two women have served as chairs of the department. Currently, our department, with its 10 women faculty, is 35% female among the tenured and tenure-track faculty. According to a 2005 survey by the Committee of the American Physical Society on the Status of Women in Physics (*1*), this statistic makes it the nation's leader among departments having more than 10 faculty members.

EUGENIE VORBURGER MIELCZAREK

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THE RECENT ARTICLE ("UNIVERSITIES URGED to improve hiring and advancement of women," A. Lawler, News of the Week, 22 Sept., p. 1712) discussing the U.S. National Academies of Science (NAS) report *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering* (*1*) highlights several crucial issues. Among these is the conclusion that the culture and institutions of science—not a lack of talent or inherent differences between men and woman—drive inequalities in hiring, promotion, and retention. A key aspect is the finding that more than half of male faculty members have a stay-at-home spouse, whereas only 10% of women faculty are in the same situation. This implies that female faculty have greater familial and/or parental responsibilities, often in conflict with essential career activities. The imbalance is addressed by recommendations in the NAS report urging universities to enact policies allowing "flexibility that faculty need across the life course" [(*1*), p. 139]. However, the situation is more complex. Often overlooked is subtle discrimination against married academic couples attempting to equalize child-rearing and other familial arrangements. For example, although many employers have generous family leave policies, they may differ for men and women, leading to substantial financial, professional, and personal costs to couples that attempt to share responsibilities. (My husband and I discovered this when our second child was born. My husband's employer, although having generous child leave policies for women, allowed only a single day of parental leave for men at the time.) Moreover, if men with substantial familial responsibilities are also promoted more slowly than women, then fewer colleagues at higher levels have faced the same difficult tradeoffs, leading to lack of appreciation for the complexity of these issues. Clearly, in addition to policies that target explicit discrimination against women, there is a need to more carefully consider how the academic culture selects against both men and women who have substantial child-rearing or other familial responsibilities.

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IN THE U.S. NATIONAL ACADEMIES OF SCIence (NAS) report *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, the 18-member panel found underrepresentation of females in academia to be "deeply troubling and

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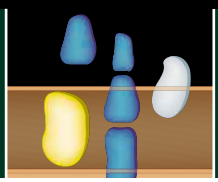

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embarrassing" ("Universities urged to improve hiring and advancement of women," A. Lawler, News of the Week, 22 Sept., p. 1712). Strangely, this 18-member panel does not find the fact that only one of its members was male to be troubling. If underrepresentation equals bias, this panel is biased by its very own criteria. In response to charges of bias, Donna Shalala, who chaired the NAS panel, pointed out to the *New York Times* (*1*) that the panel that reviewed the report had 10 males on it. On the face of it, that may seem reasonable, yet I am left asking, what if a panel of 17 men and one woman made important and far-reaching recommendations and then referred these recommendations to a gender-balanced committee for "rubber stamp" approval?

There are, in fact, cultural reasons why women are less represented in academia. Academic jobs favor individuals who are able to commit to the long hours that it takes to make it to the top. Many such individuals have stay-at-home spouses. It is a legitimate question to ask why women are so much more likely to leave the career path for the homefront. The data-driven conclusion is that women, even in higher-income brackets, tend to be married to men that make even more money on average than they do (*2*). This economic differential makes it unlikely that, when it comes time to raise children, the husband will be the one to stay home with the children. If we are really serious about recruiting women to academia, we must give female scientists honest advice. Perhaps rather than reflexively blaming every gender difference on "bias," we should be telling women to marry a man who makes less money than she does. It may be strong medicine, but recruiting the best talent demands that we examine all of the potential causes of gender imbalance.

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Property Rights and Ocean Governance

IN THEIR INSIGHTFUL POLICY FORUM "Resolving mismatches in U.S. ocean governance" (4 Aug., p. 617), L. B. Crowder and colleagues identify several key weaknesses in oceans governance. They propose "ocean zoning" to replace the current "mismatched and fragmented approaches" and ad hoc decision-making, and they provide insights into present spatial and temporal governance mismatches. To these insights can be added a third mismatch—property rights.

The importance of well-defined property rights in the success of natural resource governance (ocean- or land-based) is well recognized, as is the impact of mismatches (*1*–*3*). When mismatched property rights distributions occur, the result can be as fragmenting as those described by Crowder *et al.*

Property rights are not a unitary concept, but rather a bundle of separable rights that can be split or shared in different ways. Ostrom and Schlager (*4*) break property rights into a grouping of operational-level rights, including access (right to enter), withdrawal (right to extract), management (right to regulate use), exclusion (right to deny access), and alienation (right to sell, lease, or transfer).

Coastal fisheries resource management in New Zealand illustrates how conflicting property rights distributions can result from ad hoc decision-making [see Supporting Online Material (*5*)], yielding a pattern of fragmentation similar to that described by Crowder *et al.* Five sectors are shown, with each having a distinct bundle of rights. Property rights also can have spatial and quantitative distributions.

Unintended conflicts can result. For example, commercial fishers' right to a certain catch size can be diluted by their inability to fish in new marine reserves, resulting in greater harvesting pressure and subsequent quota cuts for stocks outside the new reserve. Here the conflict between spatially and quantitatively defined rights leads to a diminution in the value of the quantitatively defined right. In addition, poorly defined property rights

may on occasion be preferred. Recreational fishers have actively fought efforts to define their property rights, perhaps believing that poorly defined rights (but strength at the ballot box) protect their interests.

Property rights are critical to strong natural resource governance regimes. Explicitly including each sector's property rights in ocean zoning would further strengthen the proposed governance approach.

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Response

YANDLE COMMENTS THAT CONFUSED property rights in the sea can also produce fragmentation and mismatches. Of course, a comprehensive system of ocean zoning must specify the rights and obligations of users within each zone. Some activities within a particular zone may occur by right, while others may be allowed only by permit (*1*).

Fundamentally, ocean governance must rest on a clear distinction between imperium (the exercise of authority) and dominium (property rights) (*2*), a distinction ignored by Yandle. The oceans and their resources are predominately common property held in trust for the people and managed for the benefit of the public by governments of coastal nations (*3*–*5*). U.S. courts sometimes slide perilously close to the idea of the seas as private or public property, but more often, they call on the government to exercise its trust responsibility (*3*). Further, prominent scholars of ocean law have discussed priority rules applicable to resolving conflicts over the use of ocean trust resources (*6*–*8*).

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

To carry out their trust responsibilities, governments can and should exercise authority to apply the principles of ecosystem-based management (EBM). Before approving a new generation of ocean industrial facilities, governments should employ ocean zoning as a scientifically based platform for resolving conflicts among new uses as well as ongoing activities like fishing and maritime commerce.

Governments have created certain limited private rights or quasi-rights to marine resources. Some people see the solution to problems of ocean governance in wholesale privatization (*9*), but we disagree. Privatization strategies are significantly more problematic in the seas than they are on land.

We should continue to treat marine systems as common property rather than as private or public property. Understanding that the authority of the government over common property does not include the right to permanently dispose of (sell, grant, or transfer) ocean space to private owners is key to protecting the rights of the common property owners (i.e., the people). As demands for ocean resources (including exclusive access) multiply, we need management systems that protect the public interest and at the same time provide security of investment for existing and new ocean industries. The needs of private investors can be met while protecting the public trust by contracts (leases, easements, rights of way, and concessions) that ensure periodic review of performance and updating of contract terms to take into account new knowledge (regarding ecosystems and technology) (*5*).

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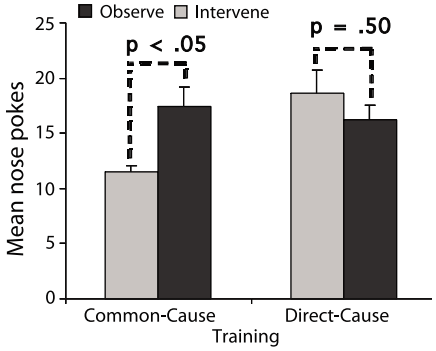
CORRECTIONS AND CLARIFICATIONS

2006 Visualization Challenge (22 Sept., p. 1729). The affiliation of one of the judges, Felice Frankel, was incorrect. It should be Senior Research Fellow, FAS, Harvard University, Initiative in Innovative Computing, IIC, Cambridge, Massachusetts. In the winning entry for the Interactive Media category, "Cerebral Vasculature of Craniopagus Conjoined Twins," the name of credited contributor Kenneth Salyer was misspelled. In the text for the second-place winner, "A Real-Time Audio and Video Sound Visualization Tool," videos were said to be available in "most" cases. In fact, they are available in "many" cases.



Reports: "Causal reasoning in rats" by A. P. Blaisdell *et al.* (17 Feb., p. 1020). The wrong input data were used to generate Fig. 1B. The corrected figure is shown here. The error does not change the conclusions of the paper.

TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Preindustrial to Modern Interdecadal Variability in Coral Reef pH"

Richard J. Matear and Ben I. McNeil

Based on the boron isotopic composition of coral from the southwestern Pacific, Pelejero *et al.* (Reports, 30 September 2005, p. 2204) suggested that natural variations in pH can modulate the impact of ocean acidification on coral reef ecosystems. We show that this claim cannot be reconciled with other marine carbon chemistry constraints and highlight problems with the authors' interpretation of the paleontologic data.

Full text at www.sciencemag.org/cgi/content/full/314/5799/595b

RESPONSE TO COMMENT ON "Preindustrial to Modern Interdecadal Variability in Coral Reef pH"

Carles Pelejero, Eva Calvo, Malcolm T. McCulloch, John F. Marshall, Michael K. Gagan, Janice M. Lough, Bradley N. Opdyke

Coral reefs are exceptional environments where changes in calcification, photosynthesis, and respiration induce large temporal variations of pH. We argue that boron isotopic variations in corals provide a robust proxy for paleo-pH which, together with the likely concomitant changes in the reconstructed partial pressure of CO_2 (Pco_2) calculated by Matear and McNeil, fall within ranges that are typical of modern coral reef ecosystems.

Full text at www.sciencemag.org/cgi/content/full/314/5799/595c

HISTORY OF SCIENCE

The Humanistic and Religious Foundations of Deep Time

Naomi Oreskes

How did we come to understand the great expanse of geological time and the complexity and subtlety of geological history? Martin Rudwick, the world's foremost historian of geology, addresses this question in *Bursting the Limits of Time*. A magisterial work, the book explains the activities and accomplishments of the men who first established that Earth had a history, one that was long, complex, and contingent. Rudwick's answer—which will surprise many readers—is that the emergence of "geohistorical thinking" had two principal sources, neither of which is to be found within the realm of what we now conventionally recognize as science. The first was human history, with its recognition that artifacts such as coins, medals, and monuments could be read as evidence of the past—an idea that segued to rocks and fossils. The second was theology, with its commitment to an unrepeated sequence of contingent past events. Rudwick's provocative thesis is that the methods, perspectives, and insights of erudite historians and biblical scholars provided the crucial resources for the emergence of modern geology.

Bursting the Limits of Time
The Reconstruction of Geohistory in the Age of Revolution

by Martin J. S. Rudwick

University of Chicago Press, Chicago, 2005. 732 pp. $35, £28.50. ISBN 0-226-73111-1.

The story begins in the late 18th century, and Rudwick paints a vivid tableau of diverse European savants addressing questions about Earth. Their research programs, pursued both indoors in museums and private collections and outdoors in the field, fell into four principal categories: mineralogy, physical geography, geognosy, and Earth physics. The first three were branches of natural history, concerned with the description and classification of things: minerals, landforms, and rock formations. The latter, as its name suggests, was dedicated to discovering the laws of nature as applied to Earth from which one might predict (or retrodict) Earth history.

None of these sciences, however, was truly historical: none offered a sense of contingent and specific development of the stages of Earth history and the life-forms that characterized them. Geognosy came the closest, as it recognized an order of rock formations linked to the progressive development of Earth; geognostic studies were a principal resource for the emergence of the "standard model" of the period, which held that gradual chemical differentiation of a global proto-ocean had produced terrestrial rock formations. Still, geognosts lacked a notion of contingent development. And while they paid some attention to fossils as distinguishing features of certain formations, few viewed them as evidence of the past, still less as documenting profound historical changes in life on Earth.

Matters changed around the turn of the century. Adamantly rejecting the Anglophone conceit that lionizes James Hutton and Charles Lyell as the founders of modern geology, Rudwick turns our attention to continental figures such as Horace-Bénédict de Saussure, Jean-André de Luc, Dieudonné de Dolomieu, Johann Friedrich Blumenbach, Georges Cuvier, Alexandre Brongniart, and Constant Prévost. Inspired by human history—in particular, the work of antiquarian historians who paid increasing attention to coins, monuments, and artifacts as direct evidence of the past civilizations that produced them—these men increasingly began to interpret rocks and fossils as evidence of Earth history. They came to consider the possibility that just as human history was highly contingent (the destructions of Herculaneum and Pompeii offering particularly vivid examples), so too might be Earth history. And just as historians began to recognize "epochs" in human history, so these savants began to recognize epochs in Earth history.

Rudwick pays particular attention to de Luc, a Genevan who served as the intellectual mentor to Queen Charlotte (the wife of England's King George III). De Luc proposed a highly influential binary system in which a long (although not infinite) ancient world, consisting of numerous epochs, was separated by a radical revolution from the modern (human) history. He also argued that the history of the ancient world, like its modern counterpart, could be reconstructed from evidence but not predicted by physical laws. Whence did de Luc obtain his commitment to an unpredictable Earth history? Rudwick's answer is "theistic apologetics." A firm believer in both God's creation and the essential (but not literal) truth of biblical revelation, de Luc struggled to account for a world consistent with Genesis. Rudwick writes:

> In taking the Creation story in Genesis as his model, he [de Luc] committed himself knowingly to an understanding of history that was radically contingent.…
>
> …[H]is explicit belief in God's sovereignty led him in practice to treat historical events as contingent, and unpredictable to mere human beings.… Transposed into the scientific realm … this implied that deterministic models of geotheory were radically misconceived. The course of events in the deep past could not possibly be predicted (or retrodicted) on the basis of any simple set of natural laws, because things might always have happened otherwise.… [G]eohistory, like human history, would have to be compiled bottom-up from the empirical evidence of how things had *in fact* happened, rather than being deduced top-down from some simple physical principles that stated how they "must" or "ought to" have happened.

While de Luc's work is mostly lost to modern geologists (although he coined the term geology), his work influenced diverse scholars, including Dolomieu, who calculated the age of the Nile delta based on observation of modern sedimentary processes; Blumenbach, who promoted the idea of geological periods characterized by distinctive fossils; Cuvier, who established the reality of extinction; Brongniart, who, with Cuvier, unraveled the history of the Paris basin by using fossils as evidence of successive and changing environments; and Prévost, who first introduced what we would recognize as the modern notion of a faunal assemblage. In short, the development of modern geology, committed to reconstructing the past from empirical evidence, was the direct result of taking seriously the very religious commitments that geology has so often been held to threaten.

Rudwick's book is a huge accomplishment—detailed, subtle, refined—and it is difficult to do justice here to the depth and breadth of its argument. It will surely stand as the definitive work on the topic for many years to come. But just for this reason, it is important to address what has been left out

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"Fearless pursuit of an Enlightened knowledge of nature." William Hamilton led the King and Queen of the Two Sicilies to view an incandescent lava flow on the flank of Vesuvius the night of 11 May 1771 [drawing by Pietro Fabris, published as a colored etching in (*4*)].

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as well as what has been put in. One potentially important omission is the question of knowledge of Earth history by individuals and groups other than Europeans and the white settlers of North America.

This is a delicate issue. Elsewhere Rudwick has argued that science, until quite recently, was an activity of European elites, and to claim otherwise is wishful thinking at best. Given the importance of elite science, it is worthy of study in its own right, without apologetics. Quite so. But what if there is evidence that European elites were influenced in their thinking by the claims of, for example, the native peoples of North America? What if their scientific conclusions in some way relied on native knowledge? Consider the case of Georges Cuvier.

Cuvier is a pivotal figure in Rudwick's narrative for his insistence that Earth history involved not simply one "former world," but a succession of former worlds each with a distinctive fauna, now extinct. But his research confronted the thorny issue of "living fossils": Mightn't these apparently extinct species still roam the unexplored hinterlands of the Americas, Africa, or Asia? The issue was crucial both for one's concept of the past and for emerging debates about organic evolution. Thomas Jefferson, for example, denied that the extremely famous "Ohio animal" (later recognized as a mastodon) was extinct, but Cuvier insisted that it was. Why was Cuvier so sure? Historian Adrienne Mayor has recently argued that native American knowledge is part of the answer.

It is well known that native Americans served as informants to European-American fossil collectors, guiding them to abundant sites. But Mayor suggests that native Americans not only knew of fossils, but recognized them as the remains of creatures that no longer existed. Oral traditions recorded by Spanish, French, and English colonists attested to native people's belief in the prior existence of now-extinct species, and Cuvier cited these traditions as part of his argument for extinction (*1*, *2*)

Mayor notes that in his magnum opus, *Recherches sur les Ossemens Fossiles de Quadrupèdes*, first published in Paris in 1812, Cuvier dedicated "some 20 pages to fossil discoveries and traditions by Native Americans gleaned from his reading and correspondence." Earlier he had remarked on "Indians' repeated assurances that no living specimens [of the Ohio animal] had ever been seen" (*2*). Mayor quotes Cuvier: "'How then can it be believed that the immense mastodons and gigantic megatheriums [sloths] whose bones are found underground in the two Americas, still live?' … How could such enormous beasts 'escape the knowledge of the nomadic peoples who move ceaselessly around the continent in all directions, and who themselves recognize that the creatures no longer exist?'" (*3*). Mayor thus concludes that "These widespread extinction scenarios, from Peru to Canada, helped Cuvier to rule out migration and focus on catastrophic extinctions, and therefore were significant in developing the theories that established the new science of paleontology" (*2*).

If Mayor is right, and native knowledge played a role in the thinking of European savants, then it suggests that our conventional notions of the boundaries of Western science may need to be readjusted. Younger scholars may thus feel content that despite all that Rudwick has accomplished in *Bursting the Limits of Time*, there is more that remains to be done.

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10.1126/science.1120239

PHYSICS

Teach the Controversy!

Aaron Pierce

Quantum mechanics and general relativity, two triumphs of 20th-century physics, do not play together well. In extreme situations where both gravity and quantum mechanics are important—as during the first instants after the Big Bang or at the center of a black hole—these otherwise extraordinarily successful theories break down and must be modified. The vast majority of particle theorists who seek to reconcile these two theories have chosen string theory as their approach.

This was not always the case. At its inception, string theory appeared plagued with inconsistencies, and few theorists considered it a likely avenue of advance. Then, in 1984 John Schwarz and Michael Green published a watershed paper that elegantly explained how the theory actually avoided these inconsistencies (*1*). Virtually overnight, string theory became the leading candidate for unifying quantum mechanics and gravity, and theorists flocked to work on it. Lee Smolin, a physicist now at the Perimeter Institute in Waterloo, Ontario, is also devoted to the problem of reconciling quantum mechanics and gravity. But, in sharp intellec-

The Trouble with Physics
The Rise of String Theory, the Fall of a Science, and What Comes Next
by Lee Smolin
Houghton Mifflin, Boston, 2006. 416 pp. $26, C$34.95. ISBN 0-618-55105-0.

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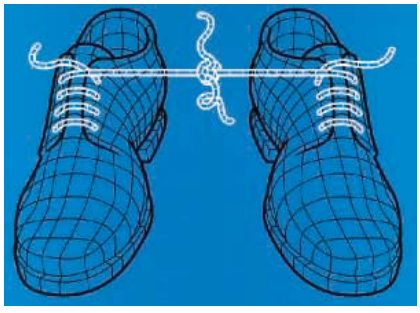
tual opposition to string theory, he favors a rival approach, loop quantum gravity, which has garnered far less attention.

Smolin's *The Trouble with Physics: The Rise of String Theory, the Fall of a Science, and What Comes Next* is not a book whose purpose is to introduce the newcomer to exciting ideas in quantum gravity; indeed, nonphysicists might find passages rough going. Rather, it is a lamentation for the bygone era when a few renegade physicists could independently develop ideas about quantum gravity and have them quickly embraced by the larger community. Smolin claims that high-energy theorists have become less receptive to radically new approaches to quantum gravity. There is an important reason for this. In 1984, there was no coherent theory of quantum gravity available. So, when Green and Schwarz made their breakthrough, string theory quickly became the front-runner. Today, the playing field is not so wide open. Any new theory of quantum gravity must compete with a widely accepted rival. And although string theory is far from proven, it does have results to which it can point. To mount a successful challenge, an alternative theory must show the promise that it can rise to a similar level. The bar has been raised.



String theory can provide a consistent, calculable theory of quantum gravity, but serious simplifying assumptions must be made to make calculations tractable. The situation is analogous to scientists' propensity to "consider a spherical cow." There is a risk that the assumption may oversimplify the problem, but it is often a good starting point. In the case of string theory, the simplifications made in these toy examples often make the model universes look vastly different from our own. To determine whether string theory is making progress requires questioning whether these toy models have robbed the universe of its bovine essence. How much weight should be given to such supportive "results"?

Following the philosopher of science Paul Feyerabend, Smolin remarks, "Different scientists adopt different viewpoints and take their chances on which one will be borne out by developments. There is no general rule for when to abandon a theory and when to keep it alive." Indeed, based on the evidence available to them, scientists must make an individual judgment on whether a theory is not worth pursuing. And because string theory has not made direct contact with our universe, there is bound to be even more haggling over the extent of progress and, for that matter, what constitutes evidence. Physicists engaged in the pursuit of a theory of quantum gravity must read the tea leaves and argue over whether their solutions to the toy models have put them on the right track.

After considered thought, the majority of physicists working on the problem of quantum gravity have concluded that string theory is the best approach available. Smolin believes this represents an unprecedented breakdown in the marketplace of ideas: string theory is so entrenched in the academy that the result is a de facto conspiracy to suppress dissenting ideas. To his mind, string theorists have too much at stake to make an unbiased assessment, and so it falls to unbiased outsiders like him to make the judgment for them. This is a bold claim.

From my experience as a theoretical physicist outside the string theory community, I find theorists who have chosen string theory over other approaches have well-reasoned physical reasons for doing so. Smolin's arguments did not convince me otherwise. And even though it is indeed true that string theorists dominate the quest for a theory of quantum gravity, the critical question is whether this dominance exceeds what is reasonable or rational. Smolin's rhetorically charged presentation might lead some readers into concluding otherwise, but a balanced assessment indicates that the marketplace of ideas in theoretical physics is alive and well.

One common attack on string theory, reiterated by Smolin, argues that it is "untestable" at current particle accelerators or even in experiments likely to be devised in the foreseeable future. But in all likelihood, this is not a foible unique to the string theory approach: it is a problem associated with all theories that seek to unify quantum mechanics and gravity. The reason is effective field theory, a concept largely pioneered by Kenneth Wilson while at Cornell University (*2*). The basic idea is that there exists a given set of particles and interactions that can effectively describe the relevant physics at any given energy scale. Indirect effects from unknown physics at higher energy scales (like the ones where string theory might be important) can largely be encoded in the apparent strengths of the interactions at lower energies. Any effects that cannot be so absorbed are strongly suppressed. As one of my former colleagues was fond of saying, effective field theory means that you don't need to know the theory of quantum gravity to make chicken soup.

In the mid-1980s, many string theorists had hoped that traditional ideas of effective field theory would break down. The oil and water of quantum mechanics and gravity could be so loath to mix that a successful combination could only be possible in a single universe—our own. If true, the mere integrity of the mathematical structure of string theory would be so constraining that it could explain why the electron weighs 0.511 MeV, why there are four known forces, and everything else about particle physics. Thus, any surprise in store at accelerators would constitute a potential verification of the theory of everything. Unfortunately, recent developments in string theory indicate that it is unlikely to be that restrictive. This decreases the prospects for testing string theory via the constraints it places on low-energy physics. In part, this explains the increase in recent attacks on string theory. Nonetheless, it is premature to completely shut the door on whether string theory will have strong implications on accessible physics. Even if it does not, effective field theory indicates that this shortcoming is likely to be present in any approach to quantum gravity. This does not mean that the question of quantum gravity is uninteresting. Reconciling the two pillars of 20th-century physics is a compelling question, worthy of serious inquiry. Smolin agrees—he ranks this as the most important question facing physics today.

There are interesting issues to be explored regarding the progression of string theory. When theories do not make firm predictions that can be falsified within days or even years, how should science proceed? How does a research community that finds itself in such a position evaluate when progress is being made? How should scientists decide on an appropriate level of resources to expend on a theory that is unlikely to be confirmed within the lifetime of any current physicist? Both mathematics and large areas of particle physics owe many ideas to string theory. How much credit should an area of inquiry get for informing and developing tools for other fields? Smolin's *The Trouble with Physics* only obliquely references these questions. It would be interesting to see them explored more fully. Meanwhile, theorists will continue to confront the thorny problem of quantum gravity with the most promising tool they can find. For the vast majority of them, this tool is string theory.

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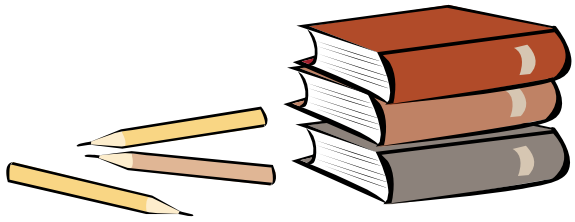
10.1126/science.1133640

DIVERSITY

Gender Similarities in Mathematics and Science



Janet Shibley Hyde[1]* and Marcia C. Linn[2]

Boys and girls have similar psychological traits and cognitive abilities; thus, a focus on factors other than gender is needed to help girls persist in mathematical and scientific career tracks.

The role of gender in mathematics and science education is hotly contested (*1*). Some advocate single-sex schooling as a way to let girls' talents blossom, freed from boys' domination in the classroom and from sexual harassment by boys (*2*, *3*). Others emphasize gender differences in learning styles, citing evidence that girls perform best under cooperative learning conditions and boys perform best in competitive learning environments (*4*). These arguments rest on the assumption that psychological gender differences are large and exist in numerous domains. Should gender be the major factor in deciding which school a child attends or which curriculum a child receives? The Gender Similarities Hypothesis (*5*) provides an alternative view, stating instead that males and females are very similar on most, but not all, psychological variables.

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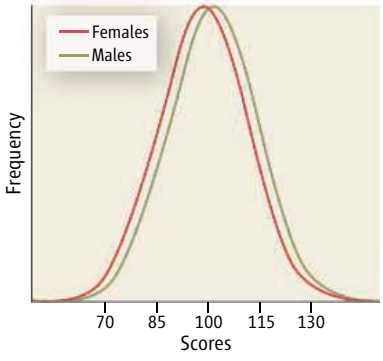
Evidence for Gender Similarities

A review of meta-analyses of research on psychological gender differences identified 46 reports, addressing a variety of psychological characteristics, including mathematical, verbal, and spatial abilities; aggression; leadership effectiveness; self-esteem; and computer use (*5*). These research syntheses summarize more than 5000 individual studies, based on the testing of approximately 7 million people. The findings are represented on a common scale based on the standard deviation. The magnitude of each gender difference was measured using the *d* statistic (*6*), $d = (M_M - M_F)/s_w$, where M_M is the mean score for males, M_F is the mean score for females, and s_w is the pooled within-sex standard deviation. The *d* statistic measures the distance between male and female means, in standard deviation units. In each individual meta-analysis, the values of *d* from multiple investigations of the same outcome were weighted by sample size and combined.

A total of 124 synthesized effect sizes resulting from meta-analysis were extracted from the reports. Following convention, *d* values in the range 0.11 to 0.35 were classified as small, 0.36 to 0.65 as moderate, and 0.66 to 1.00 as large (*6*). Values greater than 1.0 were categorized as very large and values between 0 and 0.10 were considered trivial.



Effect size of 0.20. When the effect size between two groups is 0.20, 85.3% of the distributions overlap.

Of the effects for gender differences, 30% were trivial and an additional 48% were small. That is, 78% of the effects for psychological gender differences were small or near zero. For example, for mathematics problem-solving, $d = 0.08$ (*7*); for leadership effectiveness, $d = -0.02$ (*8*); and for negotiator competitiveness, $d = 0.07$ (*9*).

An essential implication of these findings is that the overlap of distributions for males and females is substantial for most outcomes. For example, the chart above shows the distribution of male and female performance for a small effect size of 0.20. Assuming that performance fits a normal distribution (supporting online material text), for means that are 0.20 standard deviations apart ($d = 0.20$), the populations show 85.3% overlap. Only 54% of members of one gender exceed the 50th percentile for the other gender. For $d = 0.10$, there is 92.3% overlap in the distributions of the two groups, and 52% of those of one gender exceed the 50th percentile for the other. Even for a moderate effect size ($d = 0.50$), 60% of members of one gender exceed the 50th percentile for the other gender.

Most relevant here is the meta-analysis of research on gender differences in mathematics performance, which was based on 100 studies and the testing of more than 3 million people (*7*). Patterns emerged as a function of the age of test takers and the cognitive level of the test. Girls outperformed boys on computation in elementary school and middle school ($d = -0.20$). There was no gender difference in high school. There was no gender difference in deeper understanding of mathematical concepts at any age. For complex problem solving, a skill that is highly relevant for science, technology, engineering, and mathematics careers, there was no gender difference in elementary or middle school; a small difference favoring boys emerged in high school ($d = 0.29$). Consistent with these findings of gender similarities in mathematics performance, in 2001 women earned 48% of the bachelor's degrees in mathematics in the United States (*10*), demonstrating that substantial numbers of women do have the ability to engage mathematics successfully at the advanced levels required of a mathematics major.

A few exceptions to the pattern of gender similarities were identified in the review of meta-analyses. Most relevant to educational settings are the gender differences in activity level and physical aggression, with effect sizes for aggression ranging between 0.40 and 0.60 (males more aggressive) across several meta-analyses (*11*–*14*). Males display a higher activity level than females, $d = 0.49$ (*15*). It is widely believed that there are substantial gender differences in interests in fields such as psychology compared with physics, although we found no meta-analysis of this research literature.

Gender Similarities in Science

The National Assessment of Educational Progress (NAEP), the Nation's Report Card, tests thousands of students across the United States on achievement in mathematics and

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science. The conclusions from 2005 stated that males outperformed females at all three grades tested in science (*16*).

Another look at the data leads to a different conclusion. For fourth-graders, the average science score was 152.53 (SD = 32) for boys and 148.66 (SD = 30) for girls. That is, the difference is less than 4 points on a scale that ranges from 0 to 300. As NAEP reports, this gender difference is statistically significant, given the large sample size (roughly 100,000 students per grade). However, the effect size, *d*, for this gender difference is 0.12, reflecting a small difference. Increasingly large samples can detect increasingly small differences, but an assessment of the effect size, *d*, gives a more accurate reflection of the importance of the difference. Emphasis on statistical significance, while ignoring the magnitude of the effect, risks exaggerating the importance of the differences (*17*).

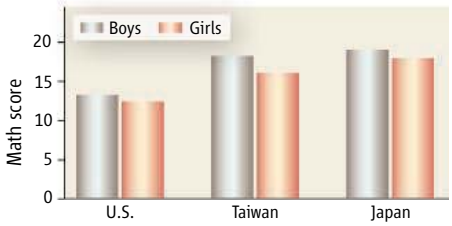
The magnitude of the gender gap in science achievement remains similar from fourth to 12th grade. NAEP reports average scores of 149.01 for boys (SD = 35) and 145.15 for girls (SD = 33) in 12th grade, for an effect size of $d = 0.11$, a small difference that is no larger than the difference in fourth grade. The NAEP data provide better evidence for gender similarities in science achievement than they do for gender differences.

Cross-National Comparisons

Cross-national data provide another way to evaluate the magnitude of gender differences in mathematics and science performance. Research on fifth-graders' performance on mathematical word problems in the United States, Taiwan, and Japan reveals a slight male advantage in each culture, but a larger difference between cultures (see chart above) (*18*). Whereas the effect size for the gender difference in the United States is $d = 0.18$, the effect size for the difference between U.S. boys and Japanese boys is $d = 1.42$. These cultural differences reflect many factors, including differences in curriculum, time spent in homework, and parents' beliefs in the importance of effort in school performance (*19*). Even within the United States, the gender difference in mathematics performance is larger in some ethnic groups than others. For whites, $d = 0.13$; whereas for blacks, $d = -0.02$; for Hispanics, $d = 0.00$; and for Asian Americans, $d = -0.09$ (*7*).

Implications

Women earn 46% of the Ph.D.'s in biology but, despite evidence for gender similarities, they earn only 25% of the Ph.D.'s in physical science and 15% in engineering. Women comprise 30% of the assistant professors in biology but only 16% in physical science and 17% in engineering (*20*). Too often, small differences in performance in the NAEP and other studies receive extensive publicity, reinforcing subtle, persistent, biases (*20*, *21*). Indeed, the magnitude of the attitudinal association between science and males is large, $d = 0.72$ (*22*, *23*). These biases can have an impact on decisions about admissions, hiring, and promotion (*24*, *25*). These biases may contribute to popular beliefs about same-sex education and learning styles, and dissuade some individuals from persisting in science (*26*).



Cross-national and gender differences in math. Differences in fifth-graders' performance on word problems are larger between countries than between genders (*18*). Boys' scores are shown in blue; girls' scores are shown in red.

For example, advocates of same-sex education claim advantages for both boys and girls (*2*). Some argue that boys' great activity level and aggressiveness make it difficult for girls to learn and participate actively, and at the same time, boys need a classroom that tolerates their active style. Activity level and physical aggression are two exceptions to the gender similarities rule, with effect sizes around 0.50 for each. Yet even a gender difference of that magnitude means that 40% of one group (in this case, girls) score higher than the average for the other group (boys). If the idea is to separate children into classrooms for the more active and aggressive and the less active and aggressive, gender is not the best indicator. A teacher's rating of activity level would be far more accurate.

The phenomenon of gender similarities has implications for schooling. Emphasis on gender differences in the popular literature reinforces stereotypes that girls lack mathematical and scientific aptitude. However, gender is a poor indicator of whether one will major in mathematics or the biological sciences as an undergraduate. A better predictor would be actual mathematics achievement scores in middle school or high school (*27*). A cultural overemphasis on gender differences may mask critical predictive variables and lead to decision-making that is empirically unsupported. To help teachers succeed, we may need to address variability in aggression and activity level for all learners. To neutralize traditional stereotypes about girls' lack of ability and interest in mathematics and science, we need to increase awareness of gender similarities. Such awareness will help mentors and advisers avoid discouraging girls from entering these fields. Continued monitoring of the relative progress of boys and girls is essential so that neither group falls behind.

Rather than focusing on gender differences, mathematics and science educators and researchers could more profitably examine ways to increase awareness of the similarities in performance and in ability to succeed.

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10.1126/science.1132154

APPLIED PHYSICS

High-Speed Atomic Force Microscopy

Innovations in engineering, miniaturization, and control-system design have the potential to allow faster imaging by atomic force microscopes.

Paul K. Hansma, Georg Schitter, Georg E. Fantner, Craig Prater

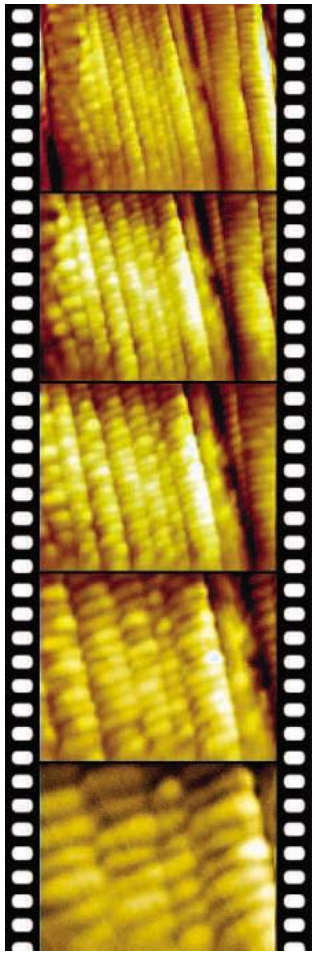
A graduate student was recently heard lamenting, "I feel like my life is passing me by!" as he waited for an atomic force microscope (AFM) image to form line-by-painstaking-line. In AFM, a sharp tip at the end of a tiny cantilever is scanned across a sample to image its topography and material properties. The images can be obtained for samples in air, water, or vacuum with typical resolution on the order of 10 nm. Despite the enormous success and widespread use of AFM, however, most users want higher speed imaging. Conventional AFMs typically take 1 to 100 min to obtain a high-quality image. The productivity and use of AFMs would increase dramatically if the speed could match the millisecond to minute image times of other scanning microscopes such as confocal and scanning electron microscopes. Moreover, there are many experiments, such as watching biological processes in liquids, that simply cannot be done without faster imaging.

The first paper on high-speed AFM was published 15 years ago (*1*). So why are faster AFMs generally not available? Just as a chain is only as strong as its weakest link, AFM speed is limited by the slowest component in its entire control loop. The achievement of high-speed scanning has required innovations in cantilevers, deflection measurement, scanners, and controllers. These innovations have pushed the state of the art in micromachining, electromechanical engineering, and control engineering.

About 10 years ago, small cantilevers (*2*) and heads for small cantilevers (*3*) were first reported. These small cantilevers can have much higher resonant frequencies at the same spring constant because their mass is much smaller. Typically the mass is smaller by a factor of 1000, making the resonant frequency higher by a factor of the square root of 1000, or about 30. The problem has been that, although individual research groups have made limited quantities (*4*–*7*), there has been no commercial source. And it has been a sort of "chicken or egg" problem: Major cantilever manufacturers have been reluctant to invest in small cantilevers because there were no commercial AFMs that could use them; AFM manufacturers have been reluctant to make small-cantilever AFMs because there were no commercially available small cantilevers. One of us (G.F.) has founded a start-up company, SCL-Sensor. Tech., to produce small cantilevers with integrated tips for this purpose.

Faster scanners are also required to take full advantage of the higher speed possible with small cantilevers. Here too, there has been substantial progress beginning with pioneering work by Ando *et al*. (*7*) and the work of Humphris *et al*. on resonant scanners (*8*). A recently reported scanner (*9*) based on finite element analysis of optimally constrained designs (*10*) achieves the necessary factor of ~30 improvement in scanner resonant frequencies in a scanner with a practical range of 13 μm in the *x* and *y* (horizontal) directions and 4.3 μm in the *z* (vertical) direction.

This leaves the control system. Here as well, substantial progress has been made both in electronics (*7*, *11*) and in control algorithms (*12*, *13*) and high-speed data acquisition (*14*, *15*). For fully functional high-speed AFM imaging, it is also necessary to increase the speed of the feedback loop that controls the height of the AFM tip by a factor of 30 to maintain minimal imaging force and high image accuracy. Fortunately, this appears within reach with emerging developments in high-speed digital electronics. For now, most of the detail in high-speed images is in the so-called error mode, such as those shown in the figure. The feedback is simply not fast enough to maintain constant cantilever deflection and accurately track the subtle details in sample topography. The information about these subtle details, such as the bands on the collagen fibrils, comes from measuring the subtle changes in cantilever deflection, which the feedback electronics are not fast enough to keep constant. The resulting images are called error mode images because they display the errors in maintaining constant cantilever deflection. As the speed of feedback increases, users increasingly will move from error mode images to quantitative topography images. Also, the imaging will be gentler because the force, which is proportional to cantilever deflection, will be kept constant.



Fast imaging. This series of images of rat tail collagen illustrates how high-speed AFM allows zooming in on areas of interest rapidly. This entire zoom series from an image width of 2 μm to a width of 470 nm was taken in 0.56 s and shows every fourth image in the series. Collagen's characteristic 67-nm banding pattern is clearly resolved in the raw data and enhanced with image processing for easy visibility. A conventional AFM would need about 15 min of imaging to obtain a comparable series of images.

In addition to relieving the tedium of waiting for images, commercial high-speed AFMs will also enable researchers to study fast processes such as protein motion (*7*, *16*) and crystal growth (*4*) and to do faster force spectroscopy (*5*) that has only been possible in a few labs with homebuilt equipment. High-speed AFM also offers enormous promise to increase the use of AFM for industrial measurements, where metrology is often monitored by the cost per measurement site. In the case where an AFM can

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operate faster by a factor of 30, this can translate into a substantially lower cost per measurement.

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10.1126/science.1133497

BIOMEDICINE

Avoiding Collateral Damage in Alzheimer's Disease Treatment

Although β-secretase has been considered a relatively harmless target for drugs against Alzheimer's disease, such drugs may damage nearby nerves.

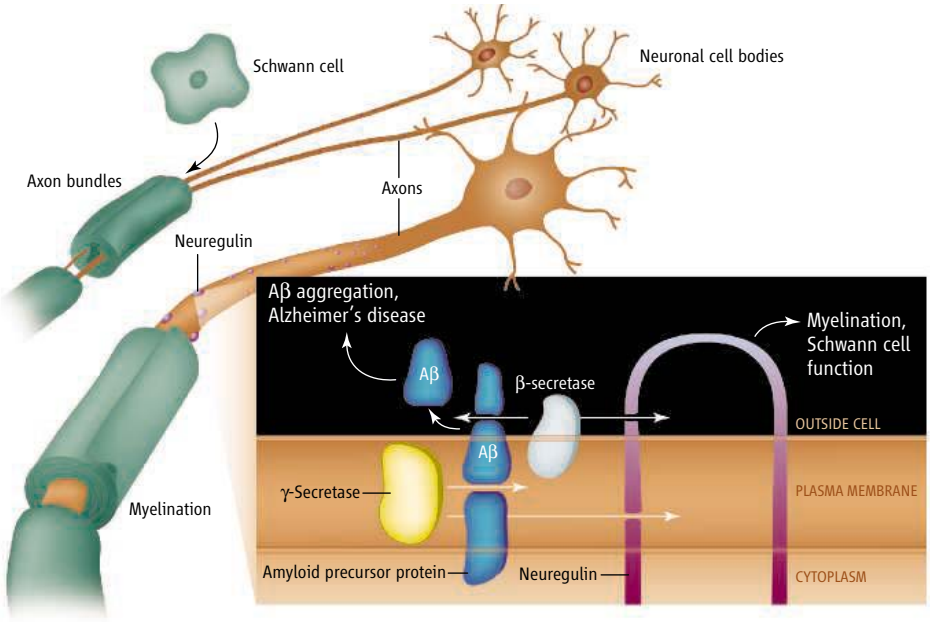
Charles Glabe

The abnormalities of Alzheimer's disease include the accumulation of a 40 to 42-residue peptide called amyloid beta (Aβ) in the brain, which eventually forms the characteristic plaques that are associated with the disease. Ever since the discovery that Aβ is generated through the proteolysis of a precursor protein, the cleaving enzymes have been considered potential targets for the development of drugs to treat the disease. In particular, BACE1 (beta-site amyloid precursor protein–cleaving enzyme 1; also called β-secretase) (*1*) has been viewed as a particularly "safe" drug target because deletion of β-secretase in transgenic mice shows no apparent detrimental side effects, although Aβ production is eliminated (*2*, *3*). But as Willem *et al.* report on page 664 in this issue, β-secretase targets another molecule that is crucial to heart development, peripheral nerve development, and neuroplasticity (*4*). This raises new concerns about the potential negative consequences of inhibiting β-secretase activity to treat Alzheimer's disease.

Aβ is genetically implicated as a causative agent in Alzheimer's disease. It is constitutively generated by proteolysis of amyloid precursor protein, a membrane protein. The proteolysis that generates Aβ occurs in two steps. First, β-secretase–mediated cleavage releases a soluble ectodomain and leaves a membrane-associated fragment. Then γ-secretase cleaves within the transmembrane domain of the latter, releasing soluble Aβ extracellularly and a soluble cytosolic fragment. As luck would have it, γ-secretase was discovered first. Mutations in presenilin, the catalytic component of γ-secretase, were associated with inherited forms of early-onset Alzheimer's disease. The mutations generally alter the cleavage site in the precursor protein, generating the longer 42-residue form of Aβ that aggregates faster (*5*). This discovery was one of the key pieces of evidence that Aβ plays a causal role in disease pathogenesis.

But there has been limited enthusiasm for γ-secretase as a drug target to decrease Aβ production. Other functions of the enzyme have proven broad and critical for normal biological processes, as transgenic mice lacking presenilin 1 and 2 have a severe developmental phenotype (*6*). Among the large number of γ-secretase substrates that have been identified are important morphogenic molecules, including Notch, Delta, and Jagged (*7*). So inhibiting γ-secretase may have a variety of unwanted side effects.

Once β-secretase was discovered, it appeared to be a more appealing drug target, as amyloid precursor protein seemed to be its only known substrate and transgenic mice lacking β-secretase displayed no obvious phenotypic aberrations. This suggested that



Myelination in jeopardy? Just like amyloid precursor protein, type III neuregulin 1 is also cleaved by β-secretase. Proteolytic cleavage of neuregulin 1 by β-secretase is critical for peripheral nerve myelination by Schwann cells. Drugs that target β-secretase could affect peripheral nerve development and function.

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β-secretase had no other essential functions. Willem *et al*. now show that β-secretase does have another substrate—type III neuregulin 1 (NRG1). NRG1 is essential to peripheral nerve myelination, in which myelin is supplied by Schwann cells to insulate axons and facilitate rapid electric transmission. A key to this discovery was the developmental expression pattern of β-secretase in mice and the finding that its activity increases during the early postnatal period, a time of extensive myelination and bundling of axons. The authors also show that type III NRG1 and β-secretase are expressed together in neurons. Myelin sheaths surrounding axons are strikingly thinner in mice lacking β-secretase (BACE1$^{-/-}$) relative to wild-type mice, and bundling of small-diameter axons is also impaired. This phenotype is also seen in mice haploinsufficient for NRG1 (*8*, *9*), which suggests that β-secretase–mediated cleavage of NGR1 may play a critical role in myelination (see the figure). Indeed, large amounts of uncleaved NRG1 accumulate in BACE1$^{-/-}$ mice.

Future work must address the question of whether the biologically active extracellular domain of type III NRG1 is merely presented by the axonal membrane to an adjacent Schwann cell after a single juxtamembrane cut by β-secretase or whether it is released from axons by some regulated dual cleavage. Work by Michailov *et al*. (*8*) and Taveggia *et al*. (*9*) have shown the importance of type III NRG1 in myelination, but, like Willem *et al*., they did not exclude dual cleavage of NRG1 that would release a fragment extracellularly. It remains to be shown whether β-secretase acts alone or in concert with other enzymes such an ADAM (a disintegrin and metalloprotease) or TACE (TNF-α converting enzyme), which are both involved in NRG1 shedding (*10*). Type III NRG1 is also a substrate for regulated intramembrane proteolysis by γ-secretase, which releases a soluble intracellular domain that is translocated into the nucleus and activates transcription (*11*).

Is there any truly safe strategy of targeting amyloid pathogenesis in Alzheimer's disease? Aβ is produced and secreted throughout life. The major pathological difference in Alzheimer's disease seems to be a change in conformation of the peptide from a random-coil monomer to a shape associated with the formation of oligomeric aggregates. Targeting these pathologically misfolded conformations may prove to be a safer strategy because they appear to be specific to the disease state.

Although this discovery of the role of β-secretase in myelination is reason for caution, pharmacological inhibition of both β-secretase and γ-secretase may still prove to be therapeutically beneficial. Partial inhibition of their proteolytic activities may be sufficient to lower the amount of Aβ to a level that may delay the onset and progression of the disease without producing intolerable side effects. Delaying the age of onset by even 5 years would have an enormous impact in lowering the incidence of disease in the population. And that seems like a risk worth taking.

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10.1126/science.1135043

BIOCHEMISTRY

Directing Biosynthesis

Michael A. Fischbach and Christopher T. Walsh

Genetic engineering is revealing biosynthetic pathways for synthesis of small molecules and avenues toward cheaper syntheses, potentially providing access to better drugs.

Long before the advent of written records, our ancestors used yeast to turn sugar into carbon dioxide and ethanol. Today, we are no longer limited to fermentation products naturally excreted by bacteria and fungi. Using the tools of genetic engineering, we can direct microorganisms to make proteins, DNA, carbohydrates, and small molecules (*1*). These "biomolecule factories" also serve as experimental systems for studying biosynthesis; in turn, such studies often facilitate efforts to manipulate biosynthetic pathways to make new products.

Projects aiming to direct the biosynthesis of small molecules may seek to make new compounds, make natural compounds in unnatural organisms, or alter the metabolic flux through a particular biosynthetic pathway. Here we use three examples to illustrate the state of the art in directed biosynthesis and highlight its future prospects.

Our first example involves the antitumor agent echinomycin from the soil bacterium *Streptomyces lasaliensis*. Like proteins, echinomycin is a polypeptide, but the similarities end there. Whereas proteins are synthesized by the ribosome, echinomycin is produced by an enormous assembly-line enzyme called a nonribosomal peptide synthetase (NRPS) (*2*). This synthetase is similar in size to a ribosome—yet it makes only a single peptide product. Many bacteria and fungi invest heavily in such synthetases, devoting more than 5% of their genome to the production of toxins, iron scavengers, and surfactants (*3*).

One difference between ribosome-synthesized proteins and nonribosomal peptides is that the latter are often cyclic rather than linear. Cyclization makes the structure of these peptides more rigid; this is usually required for their biological activity. The protein domains from NRPSs that catalyze cyclization have been used as purified enzymes to cyclize small libraries of synthetic peptides, creating unnatural derivatives of natural nonribosomal peptides (*4*, *5*).

In addition to being cyclic, echinomycin has a second conformational constraint: Two of its cysteine residues are linked by a chemical bond known as a thioether. Because thioether bonds cannot be cleaved by biological reductants, they are more stable than the cysteine-linking disulfide bonds commonly found in proteins.

To study the biosynthesis of echinomycin, Watanabe *et al.* inserted the 16 genes responsible for its production into the bacterium *Escherichia coli* (*6*). The resulting strain pro-

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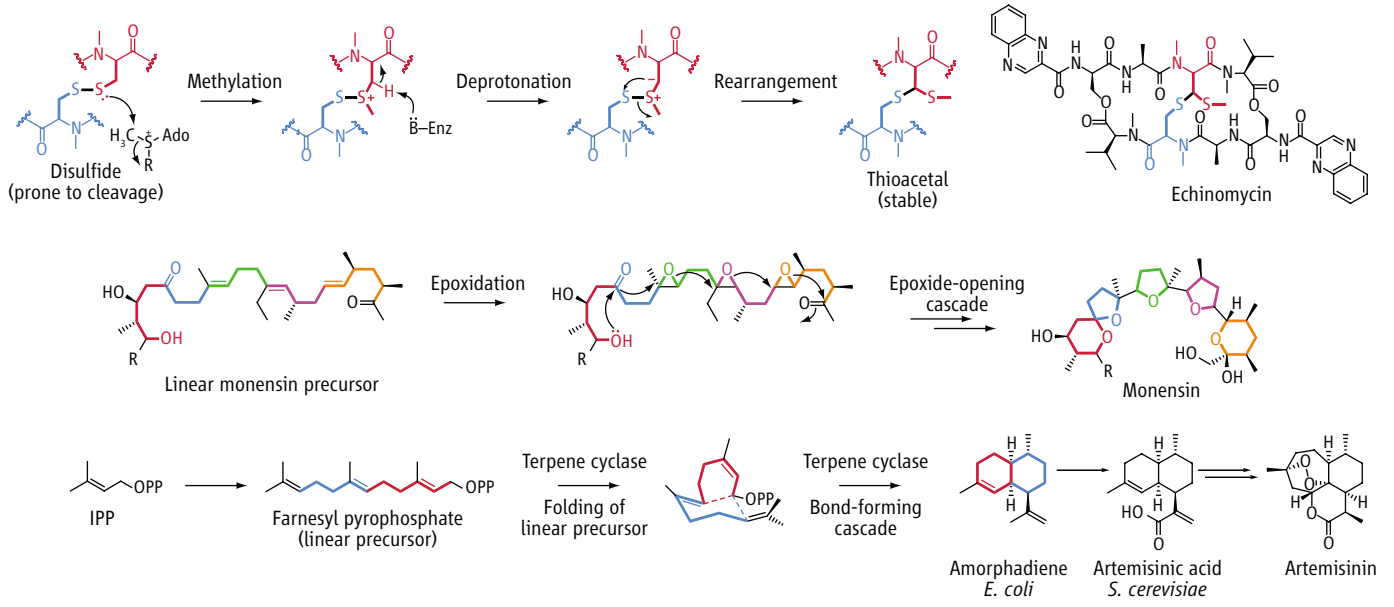

Directed biosynthetic transformations of small molecules. (Top) Formation of the thioacetal cross-link in echinomycin (*6*). Ado, adenosinel; Enz, enzyme. **(Middle)** Proposed two-step rearrangement of the linear monensin precursor to form the five rings of monensin (*9*). **(Bottom)** Formation of amorphadiene from farnesyl pyrophosphate during artemisinin biosynthesis (*10*, *11*). OPP, pyrophosphate.

duced echinomycin and set the stage for studying the formation of its thioether cross-link. In echinomycin, the thioether is embedded in a stable chemical group known as a thioacetal. The authors show that this thioacetal is formed in an unusual methylation-rearrangement sequence from two cysteine side chains initially linked by a less stable disulfide bond. This reaction sequence is catalyzed by a single enzyme (see the figure, top panel). Knowledge of this enzymatic process may enable similar cross-links to be formed in synthetic peptide drug candidates, stabilizing them against proteolysis.

The production of echinomycin in *E. coli* is also important for its future prospects as an antitumor drug. Given that *E. coli* are easy to manipulate genetically, the echinomycin NRPS could be engineered to create echinomycin analogs that would be difficult to synthesize chemically. For example, Miao *et al.* have taken advantage of the modular organization of NRPSs, replacing monomer-incorporating modules with foreign counterparts to create unnatural derivatives of their small-molecule products (*7*).

Our second example involves monensin, an antiparasitic and antibacterial agent that is used widely in cattle and chicken feed as a growth promoter. Produced by the soil bacterium *Streptomyces cinnamonensis*, monensin belongs to a family of molecules called polyethers that includes some of the deadliest poisons known (*8*). Monensin is made by a polyketide synthase; such synthases are similar to NRPSs but use building blocks derived from acetate instead of amino acids (*2*). However, the final structure of monensin—with its five oxygen-containing rings—looks very different from the linear precursor made by its synthase.

To investigate this molecular metamorphosis, Gallimore *et al.* coupled genetic evidence from *S. cinnamonensis* with biophysical analysis of a protein responsible for part of this transformation. They deduce that this complex rearrangement is probably a two-step process (see the figure, middle panel) (*9*). First, one enzyme converts the three carbon-carbon double bonds to oxygen-containing three-membered rings (epoxides). In the second step of monensin rearrangement, an enzyme initiates an epoxide-opening chain reaction that forms the five rings of monensin, dramatically reconfiguring the topology of its carbon backbone.

Unlike the module exchange and enzymatic cyclization strategies of directing nonribosomal peptide biosynthesis, knowledge of how enzymes control the epoxide-opening cascades that form polyethers remains very limited. Future investigations will show how these enzymes can be engineered to create derivatives of natural polyethers with new topologies and biological activities.

Our final example involves artemisinin, a highly effective antimalarial drug that is naturally produced by the sweet wormwood tree. Artemisinin is readily available in industrialized countries, but its supply is limited in the developing world by its high cost, due in part to the long generation time of the sweet wormwood tree and the challenge of isolating artemisinin from other small molecules produced by the tree.

To provide a cheaper, more renewable source of artemisinin, Keasling and co-workers have inserted the genes responsible for the biosynthesis of its late-stage precursors in *E. coli* and the bakers' yeast *Saccharomyces cerevisiae* (see the figure, bottom panel) (*10*, *11*). Artemisinin belongs to a class of small molecules known as terpenes, which include cholesterol, testosterone, and estrogen. All terpenes are made from the same set of linear precursor molecules, which are molded like clay into a variety of shapes by enzymes called terpene cyclases (*12*). These enzymes play the role of the potter and the kiln, first folding the linear precursor into a specific conformation and then setting off a cascade of bond-forming events that locks the shape in place.

In the case of artemisinin, a terpene cyclase folds its linear precursor into amorphadiene, a molecule with two fused six-membered rings. Because *E. coli* make very little of the terpene building block isopentenyl pyrophosphate (IPP), Keasling *et al.* enhanced production by inserting the IPP biosynthetic genes from *S. cerevisiae*. When they added a synthetic terpene cyclase gene, the resulting *E. coli* produced 24 mg/liter of this early-stage artemisinin precursor (*10*). In a promising follow-up study, the same group reconstituted the pathway one step further in *S. cerevisiae*, producing 100 mg/liter of the late-stage artemisinin precursor artemisinic acid (*11*), which can be converted to artemisinin in a simple synthetic process. This work breaks new

ground in expanding the biosynthetic capabilities of *E. coli* and *S. cerevisiae* and is a terrific example of how directed biosynthesis can be applied to solve pressing problems in the supply of small molecules.

Future advances in the directed biosynthesis of small molecules will be driven by a mixture of technology and creativity. Improvements in gene synthesis technology will facilitate the construction of increasingly large sets of genes that comprise natural and artificial biosynthetic pathways, and less costly DNA sequencing technologies will drive the expansion of sequencing projects to identify biosynthetic genes for uncharacterized small molecules. The production of small molecules in heterologous microbial hosts (*13*) will provide cost-effective sources of drugs, while engineering of biosynthetic enzymes (*14*, *15*) will provide access to a rich variety of "unnatural natural products" with improved properties or new biological activities. These advances will improve our ability to control the shape and topology of small molecules, allowing us to create new small-molecule conformers that interact specifically with biological targets.

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10.1126/science.1132692

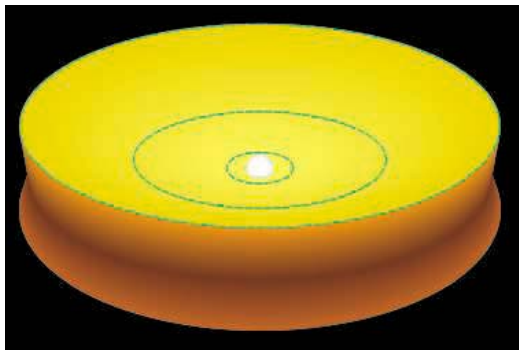
ASTRONOMY

Born with Flare

The distorted shape of a dusk disk around a young star suggests that plenty of raw material still exists, even after 3 million years, to form giant gas planets.

Charles Telesco

Almost 200 planets have been discovered around distant stars, revealing a rich and unanticipated variety among planetary systems (*1*). As unlikely as it seemed only a decade ago, we are now beginning to appreciate our own solar system as just one among many possible outcomes of planetary evolution. How much of this variety is due to normal random events in the young planetary systems and how much depends on fundamental properties of the star and the initial characteristics of the matter that formed the planets are questions at the forefront of planetary research. One can extrapolate backwards from the observed planetary configurations and dynamics to try to answer these questions, but a parallel approach is to probe planet-forming disks themselves for clues to how a planet is made. Astronomers are working furiously to discover and characterize these disks. On page 621 of this issue, Lagage *et al*. (*2*) describe their observations of a very young disk. Because it surrounds a relatively rare type of star several times as massive as the Sun, their observations provide a different perspective on the nature of possible planet-forming disks, thereby contributing to a greater understanding of the process.



Detecting a flared disk. For an arbitrary angular tilt of the flared circumstellar disk to our line of sight, circles inscribed on the bowl-like surface and concentric with the star should appear as ellipses, with the centers of the larger ellipses being more shifted away from the star. For a flat disk, the ellipses would be concentric.

The broad outlines of star and planet formation are now clear. Interstellar clouds clump and collapse, the core of each compressed knot heating up enough to fuse hydrogen and become a star, the remaining knot material settling into a disk that coalesces into planets within a few million years (*3*). Using an infrared camera on an 8-m telescope operated in Chile by the European Southern Observatory, Lagage *et al*. have imaged a disk that surrounds the star HD 97048. The infrared radiation is emitted by the disk's small solid dust particles that have been warmed by the star's ultraviolet light. The disk they see extends out to at least 370 astronomical units (AU) from the star (1 AU is the average distance of the Earth from the Sun), which is 10 times as large as the orbit of Pluto. Images of such disks around other stars have been obtained (*4*), but a combination of features makes this observation unique. HD 97048 is only about 3 million years old and thus close to the critical stage of planet formation. The star is several times as massive as our Sun, which lets us see how the possible planet-forming disk environment compares to those observed around the much more common lower-mass stars.

What makes the observation especially intriguing, however, is a distinct distortion in the image of HD 97048. There is an asymmetric brightness distribution that indicates Lagage *et al*. are seeing the surface of a tilted flared disk (see the figure). A flared disk is like a saucer that is thicker at the edge than at the center, with the surfaces on opposite sides of the saucer being bowls that face away from each other. Dust particles residing on these bowl-shaped surfaces are easily illuminated by the star located at the center of the bowl. (Lagage *et al*. actually detect very large ultraviolet-excited molecules called polycyclic aromatic hydrocarbons, or PAHs, which in many ways behave like very tiny dust grains.) If the disk is opaque, then we can see only the bowl-shaped surface tilted toward us. For an arbitrary angular tilt of the disk to our line of sight, circles inscribed on the surface of the bowl and concentric with the star appear as ellipses with their centers systematically shifted farther away from the star the larger the ellipse is, exactly as Lagage *et al*. have observed. The ellipses represent contours of constant infrared inten-

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sity. We see only one (the near) surface of the flared disk because the dust particles in the disk interior are so numerous that even infrared radiation, which is much less easily absorbed by dust than visible light, is sharply attenuated after being emitted on the far side. This high dust density and resultant high opacity are what we expect for a very young disk, where there has not been enough time for the dust to coalesce into larger bodies or be removed by stellar radiation pressure.

The fact that the dust disk is flared and not flat is important. A disk of gas assumes a particular shape that is determined by the balance of gravity, gas pressure, and turbulence. The flaring results because the component of the star's gravitational force directed toward the midplane of the disk decreases with increasing distance from the star (*5*). The infrared imaging by Lagage *et al*. detects dust particles, not gas. If there were little or no gas mixed with the dust, the particles would have collapsed very quickly to the disk midplane under the pull of gravity. The observed flaring tells us that sufficient gas must still be mixed with the observed dust, even after 3 million years, to entrain much of the dust and continually stir and elevate it above the plane. The presence of gas is a prerequisite for giant-planet formation, so even after 3 million years, there may be substantial raw material in HD 97048 for that to occur. The total amount of mass (dust plus gas) in this disk appears to be comparable to the minimum needed to make a planetary system like our own, but Lagage *et al.* conclude that conditions are probably not conducive to planet building in the disk's outer regions that they are probing. Conditions in the disk's inner region comparable in size to our solar system may be much more favorable, however.

Flared disks have been observed directly in stars less massive than the Sun, but this is the first image of a flared disk in a much more massive star. It suggests that disks and perhaps planet formation are similar for stars ranging in mass up to at least a few times that of the Sun. Conditions and time scales in circumstellar disks are thought to be a strong function of stellar mass, so these new observations will contribute to a more robust picture of disk evolution and planet formation.

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10.1126/science.1133759

NEUROSCIENCE

Charting Olfactory Maps

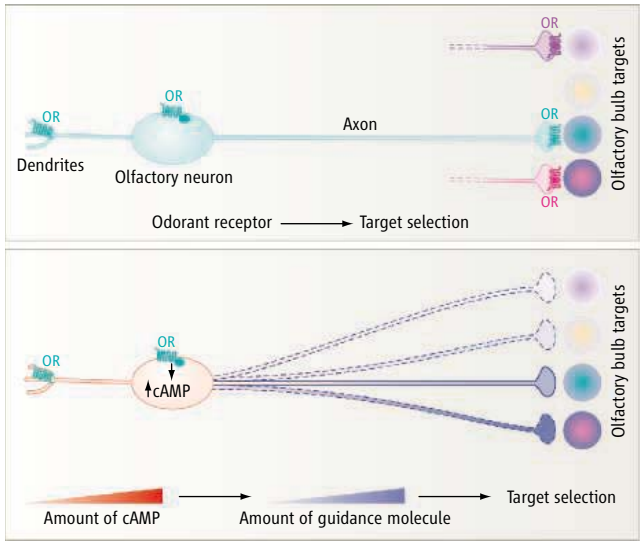
Receptors that guide olfactory neurons to the brain act not only at the starting point of signal transduction but also within the cell to trigger expression of other guidance molecules.

Catherine Dulac

We perceive the delicate fragrance of a flower or the repulsive odor of a skunk through olfactory neurons that line our nasal cavities. These sensory neurons detect specific changes in the chemical properties of the environment and transmit this information via neuronal processes (axons) that extend to the olfactory bulb in the brain. The precise wiring between neurons in the nose and in the brain ensures that we perceive the correct smell. Each olfactory neuron expresses a unique odorant receptor gene. The odorant receptor has a dual sensory and developmental function: It detects specific odors, and it plays an instructive role in the precise targeting of olfactory axons to the bulb. New evidence reported by Imai *et al*. on page 657 in this issue (*1*) suggests that odorant receptors generate intracellular signals of cyclic adenosine monophosphate (cAMP), triggering the expression of guidance molecules that are essential for proper axonal projection.

The study of the formation of sensory circuits has provided unique insights into mechanisms by which the brain achieves specificity in axon guidance and target recognition. Decades of experimental studies, mostly in the vertebrate visual system, have given rise to several general principles. As first suggested by R. W. Sperry in his chemoaffinity model in the 1960s, growing axons navigate toward their target by using specific cell surface receptors to identify environmental guidance information positioned either as discrete cues or in gradients. Further refinement to generate a precise visual map involves activity-dependent processes such as the strengthening of synaptic connections by the synchronous firing of neurons in response to a given stimulus, while inappropriate synapses are weakened and ultimately eliminated.

The development of olfactory connections has offered another opportunity to investigate the balance between activity-dependent and -independent mechanisms, and between intrinsic and extrinsic information in sensory map formation. In the olfactory epithelium of mammals, each olfactory neuron expresses only one odorant gene from a family of about 1000 genes, and all neurons expressing the same odorant receptor send precise projections to a dedicated pair of



Olfactory map formation. (**Top**) Odorant receptors in (ORS) mammals may directly guide axons of olfactory neurons to appropriate targets in the brain's olfactory bulb. (**Bottom**) Changes in the amount of cAMP in a neuron, triggered by activated odorant receptors, leads to anteroposterior shifts in axon targeting. This is associated with changes in the expression of neuropilin 1, a guidance molecule.

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glomeruli positioned in anatomically conserved locations of the olfactory bulb. How do neurons expressing a given receptor identify their target with such precision? On the one hand, it is difficult to envision a family of guidance molecules that is sufficiently diverse to account for more than 1000 discrete glomerular sites, and that is regulated in sync with the stochastic choice of odorant receptor expression. On the other hand, study of olfactory projections in genetically anosmic animals indicates that sensory activity is not required for appropriate connections to the olfactory bulb.

The intriguing observation that messenger RNAs (mRNAs) encoding odorant receptors are transported to the axon terminals of olfactory sensory neurons (*2*, *3*) led to the idea that odorant receptors may also be expressed there. Indeed, odorant receptors are detected in olfactory neuron terminals (*4*). Moreover, genetic manipulation studies indicate that the olfactory receptor ensures appropriate axon guidance. Deletion of odorant receptor coding sequences abolishes proper glomerular targeting, and substitution of specific receptor sequences leads to the convergence of axons to new glomerular targets (*5*, *6*). Interestingly, the latter results in an imperfect swap of glomerular targets, indicating that odorant receptors are unlikely to be the sole determinants of projection specificity and that other guidance receptors must also participate in the process.

The results from Imai *et al*. suggest that the odorant receptors may control the axon-guidance process only indirectly, through modulating the intracellular concentration of cAMP (see the figure). Imai *et al*. successively investigate a shift in the target of axon projections in mice in which subsets of olfactory neurons were engineered to express an odorant receptor and mutated signaling components of the G_s heterotrimeric GTP-binding protein signal transduction cascade. Odorant receptors are thought to transduce signals by activating a specific heterotrimeric G protein, Golf. However, during development of the vertebrate olfactory system, G_s is also expressed in immature olfactory neurons. Axon projections from neurons expressing a mutant odorant receptor that is unable to couple to G_s do not target glomeruli. However, this phenotype is partially rescued when an activated form of a transcription regulatory factor called CREB (cAMP response element–binding protein) is expressed. This suggests involvement of odorant receptor–driven cAMP signaling in guidance. Furthermore, when mutated or wild-type forms of an odorant receptor are expressed with constitutively active forms of G_s that generate greater amounts of cAMP, axons shift their site of projection to glomeruli located more posteriorly compared to neurons expressing just the wild-type odorant receptor. In contrast, reduced cAMP signaling (due to expression of a dominant negative form of protein kinase A) shifts glomerular projection anteriorly. These results suggest that the amount of cAMP in a neuron acts as a signal, playing a direct role in the choice of glomerular projections along the anteroposterior axis of the olfactory bulb.

What mechanism translates the intracellular concentration of cAMP into specific guidance cues? Imai *et al*. propose *neuropilin 1* as one of the candidate target genes. Neuropilin 1 is an axon guidance molecule whose expression at the cell surface is regulated by cAMP and distributed in a gradient along the anteroposterior axis of the olfactory bulb nerve layer.

A novel hypothesis thus emerges in which the odorant receptor is not at the front line of the olfactory-guidance process but instead controls the function of discrete guidance molecules such as neuropilin 1 through an intracellular signaling cascade. A corollary of this model is that each odorant receptor generates a discrete cAMP signal, which in turn modulates control of transcription by CREB, but direct proof of this awaits further investigation.

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10.1126/science.1135139

OCEANS

New Pieces for the Marine Sulfur Cycle Jigsaw

Gill Malin

It was thought that phytoplankton make DMSP, a key compound in the marine sulfur cycle, whereas bacteria use it. Now, one study shows that diatoms can also take up DMSP; another study identifies a key bacterial gene involved in its demethylation.

Sulfur—a vital nutrient for all living organisms—is abundant in the oceans but scarce on land. More than 30 years ago, Lovelock *et al*. (*1*) proposed that sulfur is transported to the land via emissions of the volatile compound dimethylsulfide (DMS) from the oceans. We now know that the marine sulfur cycle is highly complex, with DMS and related compounds playing a central role. DMS-derived sulfate aerosol particles may also cool the climate by reflecting solar radiation back into space and by promoting cloud formation or modifying cloud properties (*2*).

The marine sulfur cycle jigsaw lacks a "picture on the box" guide, but many pieces have already been identified (see the figure). Two papers in this issue (*3*, *4*) bring exciting new pieces to the puzzle, advancing our understanding of the processes that influence how much DMS is emitted to the air.

Marine phytoplankton play a critical role in the sulfur cycle, because they assimilate sulfate from seawater. Some key phytoplankton groups can also make the DMS precursor dimethylsulfoniopropionate (DMSP). This compound acts as a compatible solute, an antioxidant, a metabolic overflow product, and even an information-conveying chemical in grazing interactions (*5*–*7*). Following the natural death of phytoplankton or their demise due to grazing or virus infection, DMSP spills into the surrounding seawater. The fate of this liberated DMSP is crucial, because assimilation without DMS production cancels its climate cooling potential.

DMSP is an important source of carbon and sulfur for a wide range of marine heterotrophic bacteria (*8*) and for the widespread photosynthetic cyanobacterium *Synechococcus* (*9*). On page 652, Vila-Costa *et al*. (*3*) show that the prokaryote

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Prochlorococcus and many eukaryotic phytoplankton, including diatoms, also assimilate DMSP. When they incubated natural seawater in the daylight (but without ultraviolet radiation), plankton larger than 0.6 μm in diameter took up 50 to 70% of the DMSP. In contrast, in dark incubations, virtually all uptake was due to heterotrophic bacteria. Maximal uptake activity was measured in the summer, and uptake varied in tune with increases in the ratio of DMSP to chlorophyll a.

This research brings an unexpected new piece to the puzzle. Unicellular cyanobacteria and diatoms are responsible for a substantial share of global primary production. Diatoms are an important component of the "biological pump" that moves carbon from the surface ocean to its depths. However, they have not been popular targets for DMS-related research because of their low DMSP content. The findings of Vila-Costa *et al*., together with evidence that the DMSP content of a model diatom species increases dramatically under stress conditions (*6*), highlight the need to reassess the role of diatoms in the marine sulfur cycle.

The use of molecular techniques has opened up a new era in research on marine plankton, providing fresh insights into biodiversity, physiology, ecology, and biogeochemistry. Surprisingly, though, no genes involved in bacterial catabolism of DMSP had been cloned or characterized. The work of Howard *et al*. on page 649 (*4*) is therefore a welcome advance. The authors studied a Roseobacter strain, *Silicibacter pomeroyi*, that demethylates DMSP. They identified a gene, *dmdA*, that encodes a glycine cleavage T-family protein. This enzyme catalyzes the vital first step in the demethylation pathway by removing a methyl group from DMSP. *S. pomeroyi* cultures appear to demethylate and lyse DMSP at the same time, although the yield of DMS was about 80 times higher than that of methanethiol [see figure S2 in (*4*)].

It will be important to establish how the competition between these two DMSP utilization pathways is regulated in bacterioplankton in seawater, where DMSP concentrations are usually in the nanomolar range. By searching DNA databases, Howard *et al.* found *dmdA*-like genes in other bacteria from the Roseobacter and SAR11 taxonomic groups, as well as matches in three marine metagenomes. These bacterial groups are present in the oceans in staggering numbers, and the authors suggest that a third of all bacterioplankton in surface waters might be able to demethylate DMSP.

Connecting pieces. This figure shows some of the seawater-phase parameters and processes that form the marine sulfur cycle jigsaw. The key challenge is to connect enough pieces into a model that reliably predicts DMS emissions to the atmosphere.

The challenge now is to determine how these new and important observations fit into the bigger picture. The fate of DMSP is paramount for the marine sulfur cycle; demethylation and subsequent transformation of DMS to nonvolatile products lessen the potential for the DMS climate-cooling effect. Only a fraction of the DMSP produced by marine phytoplankton ever makes it into the air as DMS—yet this sustains an annual flux of between 15×10^{12} g and 33×10^{12} g of sulfur (*10*).

Vila-Costa *et al.* show that a wide range of phytoplankton take up DMSP, which confronts the general idea that most of the DMSP in seawater is packaged inside the phytoplankton that make it. The light enhancement of DMSP uptake they observe also suggests the potential for variation in DMSP assimilation over the natural light-dark cycle. However, many questions remain. For instance, is the ability to synthesize DMSP and assimilate it from seawater common among diatoms and other eukaryotic phytoplankton? How do they regulate the DMSP uptake and synthesis pathways? And is the DMSP that is taken up incorporated into phytoplankton biomass or eventually released back into seawater?

The discovery of a key gene for DMSP demethylation by Howard *et al.* opens the way for studies of this process that use a molecular approach. Progress reported by other researchers at a recent meeting (*11*) raises the hope that we should soon also have detailed information for bacterial genes involved in DMS-removal and DMS-release pathways. With the prospect of a suite of molecular techniques for DMS-related research on the horizon, it will be possible to delve deeper into the diversity of the genes and enzymes involved in the metabolism of DMSP and DMS. We will be able to study the plankton-related pieces of the marine sulfur cycle jigsaw puzzle in much greater detail than was ever possible before.

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10.1126/science.1133279

SCIENCE COMMUNICATION

In Arctic Alaska, Climate Warming Threatens a Village and Its Culture

SHISHMAREF, Alaska—Not so many years ago, this small Alaskan village was firmly in winter's grip by the end of October. Snows would cover the ground, and temperatures would plunge low enough to freeze the Chukchi Sea. But in recent years, winter seems to come later and later—and for the Inupiaq people who live here, that's just one sign of a dramatic climate change that now threatens the future of their island community.

Shishmaref and its people will be a central focus in a new AAAS video set to debut at a special town hall event on climate change on Sunday 18 February 2007 during the AAAS Annual Meeting in San Francisco. [Learn more at www.aaas.org/climate_change.html.]

"Highlighting our plight during this conference will help our community convince the world that climate change is happening faster here in the Arctic than elsewhere in the world," said Tony Weyiouanna Sr., the village transportation planner.

The AAAS climate-change event will bring together teachers, students, policy-makers, business leaders, and some of the world's top climate researchers for presentations and dialogue on the science and expected impact of global warming. It will be moderated by AAAS President John P. Holdren, director of the Woods Hole Research Center and the Teresa and John Heinz Professor of Environmental Policy at Harvard University.

"One of the characteristics of global climate change is that the climate changes more rapidly at the high latitudes, particularly in the far North," Holdren said in an interview. "These regions around the Arctic are like the coal miner's canary, the early warning to the rest of us of the extent to which the Earth's climate is changing."

Ginger Pinholster, director of the AAAS Office of Public Programs, said the event will focus especially on the human impact of global climate change. And in Shishmaref, she said, "the impact on people is indisputable."

The Alaska Climate Research Center reports that average temperatures in Alaska have increased by 3.5 degrees Fahrenheit over the last five decades, and 6.3 degrees in winter. Glaciers are melting, causing sea levels to rise. A 2003 report by the U.S. Government Accountability Office listed 186 Alaska Native villages vulnerable to flooding and erosion, in part as a result of warming temperatures. AAAS sent a crew of three to Shishmaref in September for interviews and fact-gathering.

A Shishmaref home tumbled onto the beach after rising seas undermined the bluff where it sat.

Its 570 residents—living on a spit of sand a quarter-mile wide and three miles long, just 20 miles south of the Arctic Circle—are grappling daily with the changing climate. Where rising seas churn against melting permafrost, erosion causes extensive damage.

Tony Weyiouanna Sr. and Mayor Stanley Tocktoo

Village officials say that since 2001, the island has lost an average of nearly 23 feet of shoreline per year. Some buildings have literally fallen into the sea. Others have been moved back from the shoreline. Erosion control already has cost millions, but still, every big storm washes more land into the sea.

While the erosion and structural damage are plainly visible, village elders described how the rising seas are putting their culture at risk, too. The Inupiaq people have lived here for some 4,000 years, subsisting on the bounty of nearby seas, rivers, and fields, but now animal and bird migration patterns are changing. Even the ice is different.

When Mayor Stanley Tocktoo was a boy, the mid-winter ice was mainly blue, which meant it was thick and solid. "Nowadays," he said, "we go out a couple of miles, you have this creamy-looking ice and dark-looking ice, which is very thin and unstable."

While village leaders are working on an ambitious—and expensive—effort to relocate the entire community to the mainland nearby, Shishmaref schoolchildren as young as five are learning about the shift in the climate that will change their lives.

"I don't believe there's an age that they're too young to study climate change," said science teacher Ken Stenek. "These kids are our future. They're our future leaders. And as this community prepares to relocate, these kids are the ones that are going to be a major part of that."

AAAS

Council Reminder

The next meeting of the AAAS Council will take place during the Annual Meeting and will begin at 9:00 a.m. on 18 February 2007 in San Francisco, California, in the Imperial Ballroom of the Hilton San Francisco.

Individuals or organizations wishing to present proposals or resolutions for possible consideration by the Council should submit them in written form to AAAS Chief Executive Officer Alan Leshner by 15 November 2006. This will allow time for them to be considered by the Committee on Council Affairs at their fall meeting.

Items should be consistent with AAAS's objectives and be appropriate for consideration by the Council. Resolutions should be in the traditional format, beginning with "Whereas" statements and ending with "Therefore be it resolved."

The Economics of Information Security

Ross Anderson* and Tyler Moore

The economics of information security has recently become a thriving and fast-moving discipline. As distributed systems are assembled from machines belonging to principals with divergent interests, we find that incentives are becoming as important as technical design in achieving dependability. The new field provides valuable insights not just into "security" topics (such as bugs, spam, phishing, and law enforcement strategy) but into more general areas such as the design of peer-to-peer systems, the optimal balance of effort by programmers and testers, why privacy gets eroded, and the politics of digital rights management.

Over the past 6 years, people have realized that security failure is caused at least as often by bad incentives as by bad design. Systems are particularly prone to failure when the person guarding them is not the person who suffers when they fail. The growing use of security mechanisms to enable one system user to exert power over another user, rather than simply to exclude people who should not be users at all, introduces many strategic and policy issues. The tools and concepts of game theory and microeconomic theory are becoming just as important as the mathematics of cryptography to the security engineer.

We review recent results and live research challenges in the economics of information security. As the discipline is still young, our goal in this review is to present several promising applications of economic theories and ideas to practical information security problems rather than to enumerate the many established results. We first consider misaligned incentives in the design and deployment of computer systems. Next, we study the impact of externalities: Network insecurity is somewhat like air pollution or traffic congestion, in that people who connect insecure machines to the Internet do not bear the full consequences of their actions.

The difficulty in measuring information security risks presents another challenge: These risks cannot be managed better until they can be measured better. Insecure software dominates the market for the simple reason that most users cannot distinguish it from secure software; thus, developers are not compensated for costly efforts to strengthen their code. However, markets for vulnerabilities can be used to quantify software security, thereby rewarding good programming practices and punishing bad ones. Insuring against attacks could also provide metrics by building a pool of data for valuing risks. However, local and global correlations exhibited by different attack types largely determine what sort of insurance markets are feasible. Information security mechanisms or failures can create, destroy, or distort other markets; digital rights management (DRM) in online music and commodity software markets provides a topical example.

Economic factors also explain many challenges to personal privacy. Discriminatory pricing—which is economically efficient but socially controversial—is simultaneously made more attractive to merchants and easier to implement because of technological advances. We conclude by discussing a fledgling research effort: examining the security impact of network structure on interactions, reliability, and robustness.

Misaligned Incentives

One of the observations that drove initial interest in information security economics came from banking. In the United States, banks are generally liable for the costs of card fraud; when a customer disputes a transaction, the bank either must show that the customer is trying to cheat or must offer a refund. In the United Kingdom, the banks had a much easier ride: They generally got away with claiming that their automated teller machine (ATM) system was "secure," so a customer who complained must be mistaken or lying. "Lucky bankers," one might think; yet UK banks spent more on security and suffered more fraud. How could this be? It appears to have been what economists call a moral hazard effect: UK bank staff knew that customer complaints would not be taken seriously, so they became lazy and careless. This situation led to an avalanche of fraud (*1*).

In 2000, Varian made a similar key observation about the antivirus software market. People did not spend as much on protecting their computers as they might have. Why not? At that time, a typical virus payload was a service-denial attack against the Web site of a company such as Microsoft. Although a rational consumer might well spend $20 to prevent a virus from trashing his hard disk, he might not do so just to prevent an attack on someone else (*2*).

Legal theorists have long known that liability should be assigned to the party that can best manage the risk. Yet everywhere we look, we see online risks allocated poorly, resulting in privacy failures and protracted regulatory tussles. For instance, medical records systems are bought by hospital directors and insurance companies, whose interests in account management, cost control, and research are not well aligned with the patients' interests in privacy. Incentives can also influence attack and defense strategies. In economic theory, a hidden action problem arises when two parties wish to transact but one party can take unobservable actions that affect the outcome. The classic example comes from insurance, where the insured party may behave recklessly (increasing the likelihood of a claim) because the insurance company cannot observe his or her behavior.

We can use such economic concepts to classify computer security problems (*3*). Routers can quietly drop selected packets or falsify responses to routing requests; nodes can redirect network traffic to eavesdrop on conversations; and players in file-sharing systems can hide whether they have chosen to share with others, so some may "free-ride" rather than help to sustain the system. In such hidden-action attacks, some nodes can hide malicious or antisocial behavior from others. Once the problem is seen in this light, designers can structure interactions to minimize the capacity for hidden action or to make it easy to enforce suitable contracts.

This helps to explain the evolution of peer-to-peer systems over the past 10 years. Early systems proposed by academics, such as Eternity, Freenet, Chord, Pastry, and OceanStore, required users to serve a random selection of files from across the network. These systems were never widely adopted by users. Later systems that succeeded in attracting very many users, like Gnutella and Kazaa, instead allow peer nodes to serve content they have downloaded for their personal use, without burdening them with others' files. The comparison between these architectures originally focused on purely technical aspects: the costs of search, retrieval, communications, and storage. However, it turns out that incentives matter here too.

First, a system structured as an association of clubs reduces the potential for hidden action; club members are more likely to be able to assess correctly which members are contributing. Second, clubs might have quite divergent interests. Although peer-to-peer systems are now thought of as mechanisms for sharing music, early systems were designed for censorship resistance. A system might serve a number of quite different groups—maybe Chinese dissidents, critics of Scientology, or aficionados of sadomasochistic imagery that is legal in California but banned in Tennessee. Early peer-to-peer systems required such users to serve each other's files, so that they ended up protecting each other's free speech. One question to consider is whether such groups might not fight harder to defend their own colleagues, rather than people involved in struggles in which they had no interest and where they might even be disposed to side with the censor.

Danezis and Anderson introduced the Red-Blue model to analyze this phenomenon (*4*). Each node has a preference among resource types—for instance, left-leaning versus right-leaning political

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manuscripts—whereas a censor who attacks the network will try to impose a particular preference, thereby meeting the approval of some nodes but not others. The model proceeds as a multiround game in which nodes set defense budgets that affect the probability that they will defeat or be overwhelmed by the censor. Under reasonable assumptions, the authors show that diversity (where each node stores its preferred resource mix) performs better under attack than does solidarity (where each node stores the same resource mix, which is not usually its preference). Diversity makes nodes willing to allocate higher defense budgets; the greater the diversity, the more quickly solidarity will crumble in the face of attack. This model sheds light on the more general problem of the trade-offs between diversity and solidarity, and on the related social policy issue of the extent to which the growing diversity of modern societies is in tension with the solidarity on which modern welfare systems are founded (*5*).

Security as an Externality

Information industries are characterized by many different types of externalities, where individuals' actions have side effects on others. The software industry tends toward dominant firms, thanks in large part to the benefits of interoperability. Economists call this a network externality: A larger network, or a community of software users, is more valuable to each of its members. Selecting an operating system depends not only on its features and performance but also on the number of other people who have already made the same choice; for example, more third-party software is available for more popular platforms. This not only helps to explain the rise and dominance of operating systems, from System/360 through Windows to Symbian, and of music platforms such as iTunes; it also helps to explain the typical pattern of security flaws. Put simply, while a platform vendor is building market dominance, it must appeal to vendors of complementary products as well as to its direct customers; not only does this divert energy that might be spent on securing the platform, but security could get in the way by making life harder for the complementers. So platform vendors commonly ignore security in the beginning, as they are building their market position; later, once they have captured a lucrative market, they add excessive security in order to lock their customers in tightly (*6*).

Further externalities can be found when we analyze security investment, as protection often depends on the efforts of many principals. Budgets generally depend on the manner in which individuals' investments translate to outcomes, but the impact of security investment often depends not only on the investor's own decisions but also on the decisions of others.

Consider a medieval city. If the main threat is a siege, and each family is responsible for maintaining and guarding one stretch of the wall, then the city's security will depend on the efforts of the laziest and most cowardly family. If, however, disputes are settled by single combat between champions, then its security depends on the strength and courage of its most valiant knight. But if wars are a matter of attrition, then it is the sum of all the citizens' efforts that matters.

System reliability is no different; it can depend on the sum of individual efforts, the minimum effort anyone makes, or the maximum effort anyone makes. Program correctness can depend on minimum effort (the most careless programmer introducing a vulnerability), whereas software validation and vulnerability testing might depend on the sum of everyone's efforts. There can also be cases where security depends on the best effort—the actions taken by an individual champion. A simple model by Varian provides interesting results when players choose their effort levels independently (*7*). Each player's cost is the effort expended in defense, whereas the expected benefit to players is the probability that the system avoids failure. When this probability is a function of the sum of individual efforts, system reliability depends on the agent with the highest benefit-cost ratio, and all other agents free-ride.

In the minimum-effort case, the agent with the lowest benefit-cost ratio dominates. As more agents are added, systems become increasingly reliable in the total-effort case but increasingly unreliable in the weakest-link case. What are the implications? One is that software companies should hire more software testers and fewer (but more competent) programmers.

Work such as this has inspired other researchers to consider interdependent risk. A recent influential model by Kunreuther and Heal notes that security investments can be strategic complements: An individual taking protective measures creates positive externalities for others that in turn may discourage their own investment (*8*). This result has implications far beyond information security. The decision by one apartment owner to install a sprinkler system that minimizes the risk of fire damage will affect the decisions of his neighbors; airlines may decide not to screen luggage transferred from other carriers that are believed to be careful with security; and people thinking of vaccinating their children against a contagious disease may choose to free-ride off the herd immunity instead. In each case, several widely varying equilibrium outcomes are possible, from complete adoption to total refusal, depending on the levels of coordination between principals.

Katz and Shapiro famously analyzed how network externalities influence the adoption of technology: they lead to the classical S-shaped adoption curve, in which slow early adoption gives way to rapid deployment once the number of users reaches some critical mass (*9*). Network effects can also influence the initial deployment of security technology. The benefit that a protection technology provides may depend on the number of users that adopt it. The cost may be greater than the benefit until a minimum number of players adopt; if everyone waits for others to go first, the technology never gets deployed. Ozment and Schechter recently analyzed different approaches for overcoming such bootstrapping problems (*10*).

This challenge is particularly topical. A number of core Internet protocols, such as DNS and routing, are considered insecure. More secure protocols exist (e.g., DNSSEC, S-BGP); the challenge is to get them adopted. Two security protocols that have already been widely deployed, SSH and IPsec, both overcame the bootstrapping problem by providing adopting firms with internal benefits. Thus, adoption could be done one firm at a time, rather than needing most organizations to move at once. The deployment of fax machines also occurred through this mechanism: Companies initially bought fax machines to connect their own offices.

Economics of Vulnerabilities

There has been a vigorous debate between software vendors and security researchers over whether actively seeking and disclosing vulnerabilities is socially desirable. Rescorla has argued that for software with many latent vulnerabilities (e.g., Windows), removing one bug makes little difference to the likelihood of an attacker finding another one later (*11*). Because exploits are often based on vulnerabilities inferred from patches or security advisories, he argued against disclosure and frequent patching unless the same vulnerabilities are likely to be rediscovered later. Ozment found that for FreeBSD, a popular UNIX operating system that forms the core of Apple OS X, vulnerabilities are indeed likely to be rediscovered (*12*). Ozment and Schechter also found that the rate at which unique vulnerabilities were disclosed for the core and unchanged FreeBSD operating system has decreased over a 6-year period (*13*). These findings suggest that vulnerability disclosure can improve system security over the long term.

Vulnerability disclosure also helps to give vendors an incentive to fix bugs in subsequent product releases (*14*). Arora *et al.* have shown through quantitative analysis that public disclosure made vendors respond with fixes more quickly; the number of attacks increased, but the number of reported vulnerabilities declined over time (*15*).

This discussion raises a more fundamental question: Why do so many vulnerabilities exist in the first place? Surely, if companies want secure products, then secure software will dominate the marketplace. But experience tells us that this is not the case; most commercial software contains design and implementation flaws that could have easily been prevented. Although vendors are capable of creating more secure software, the economics of the software industry provide them with little incentive to do so (*6*). In many markets, the attitude of "ship it Tuesday and get it right by version 3" is perfectly rational behavior. Consumers generally reward vendors for adding features, for being first to market, or for being dominant in an existing market—and especially so in platform markets with network externalities. These motivations clash with the task of writing more secure software, which requires time-consuming testing and a focus on simplicity.

Another aspect of vendors' lack of motivation is that the software market is a "market for lemons" (*6*). In a Nobel prize–winning work, economist George Akerlof employed the used car market as a metaphor for a market with asymmetric information (*16*). He imagined a town in which 50 good used cars (worth $2000 each) are for sale, along with 50 "lemons" (worth $1000 each). The sellers know the difference but the buyers do not. What will be the market-clearing price? One might initially think $1500, but at that price no one with a good car will offer it for sale, so the market price will quickly end up near $1000. Because buyers are unwilling to pay a premium for quality they cannot measure, only low-quality used cars are available for sale.

The software market suffers from the same information asymmetry. Vendors may make claims about the security of their products, but buyers have no reason to trust them. In many cases, even the vendor does not know how secure its software is. So buyers have no reason to pay more for protection, and vendors are disinclined to invest in it. How can this be tackled?

There are two developing approaches to obtaining accurate measures of software security: vulnerability markets and insurance. Vulnerability markets help buyers and sellers to establish the actual cost of finding a vulnerability in software, which is a reasonable proxy for software security. Originally, some standards specified a minimum cost of various kinds of technical compromise; one example is banking standards for point-of-sale terminals (*17*). Then Schechter proposed open markets for reports of previously undiscovered vulnerabilities (*18*). Two firms, iDefense and Tipping Point, are now openly buying vulnerabilities, so a market actually exists (unfortunately, the prices are not published). Their business model is to provide vulnerability data simultaneously to their customers and to the vendor of the affected product, so that their customers can update their firewalls before anyone else. However, the incentives in this model are suboptimal: Bug-market organizations might increase the value of their product by leaking vulnerability information to harm nonsubscribers (*19*).

Several variations on vulnerability markets have been proposed. Böhme has argued that software derivatives are a better tool than markets for the measurement of software security (*20*). Here, security professionals can reach a price consensus on the level of security for a product. Contracts for software could be issued in pairs; the first pays a fixed value if no vulnerability is found in a program by a specific date, and the second pays another value if vulnerabilities are found. If these contracts can be traded, then their price will reflect the consensus on the program. Software vendors, software company investors, and insurance companies could use such derivatives to hedge risks. A third possibility, offered by Ozment, is to design a vulnerability market as an auction (*21*).

One criticism of all market-based approaches is that they might increase the number of identified vulnerabilities by compensating people who would otherwise not search for flaws. Thus, some care must be exercised in designing them.

An alternative approach is to rely on insurers. The argument is that underwriters assign premiums based on a firm's information technology (IT) infrastructure and the processes by which it is managed. Their assessment may result in advice on best practice and, over the long run, they amass a pool of data by which they can value risks more accurately. Right now, however, the cyber-insurance market is both underdeveloped and underused. Why could this be?

One reason, according to Böhme and Kataria (*22*), is the problem of interdependent risk, which takes at least two forms. A firm's IT infrastructure is connected to other entities, so its efforts may be undermined by failures elsewhere. Cyber-attacks also often exploit a vulnerability in a system used by many firms. This interdependence makes certain cyber-risks unattractive to insurers—particularly those where the risk is globally rather than locally correlated, such as worm and virus attacks, and systemic risks such as Y2K. Many writers have called for software risks to be transferred to the vendors; but if this were the law, it is unlikely that Microsoft would be able to buy insurance. So far, vendors have succeeded in dumping most software risks, but this outcome is also far from being socially optimal. Even at the level of customer firms, correlated risk makes firms underinvest in both security technology and cyber-insurance (*23*). Insurance companies must charge higher premiums, so cyber-insurance markets lack the volume and liquidity to become efficient.

Insurance is not the only market affected by information security. Some very high-profile debates have centered on DRM; record companies have pushed for years for DRM to be incorporated into computers and consumer electronics, whereas digital-rights activists have opposed them. What light can security economics shed on this debate?

Varian presented a surprising result in January 2005 (*24*): that stronger DRM would help system vendors more than it would help the music industry, because the computer industry is more concentrated (with only three serious suppliers of DRM platforms: Microsoft, Sony, and the dominant firm, Apple). The content industry scoffed, but by the end of 2005 music publishers were protesting that Apple was getting an unreasonably large share of the cash from online music sales. As power in the supply chain moved from the music majors to the platform vendors, so power in the music industry appears to be shifting from the majors to the independents, just as airline deregulation has favored aircraft makers and low-cost airlines. This is a striking demonstration of the predictive power of economic analysis.

There are other interesting market failures. Recently, for example, a number of organizations have set up certification services to vouch for the quality of software products or Web sites. The aim has been twofold: to overcome public wariness about electronic commerce, and by self-regulation to forestall more expensive regulation by the government. But certification markets can easily be ruined by a race to the bottom; dubious companies are more likely to buy certificates than reputable ones, and even ordinary companies may shop around for the easiest deal. Edelman has shown that such "adverse selection" is really happening (*25*): Whereas some 3% of Web sites are malicious, some 8% of Web sites with certification from one large vendor are malicious. He also discovered inconsistencies between ordinary Web search results and those from paid advertising: Whereas 2.73% of companies ranked at the top in a Web search were bad, 4.44% of companies who had bought ads from the search engine were bad. His conclusion: "Don't click on ads."

Economics of Privacy

The persistent erosion of personal privacy with advances in technology has frustrated policy people and practitioners alike. Privacy-enhancing technologies have been offered for sale, yet most have failed in the marketplace. Again, economics explains this better than technical factors do.

Odlyzko has argued that privacy erosion is a consequence of the desire to charge different prices for similar services (*26*). Technology is increasing both the incentives and the opportunities for discriminatory pricing. Companies can mine online purchases and interactions for data revealing individuals' willingness to pay. The results are the complex and ever-changing prices charged for such commodities as airline seats, software, and telecommunications services. Such differential pricing is economically efficient but is increasingly resented. Acquisti and Varian analyzed the market conditions under which first-degree price discrimination can actually be profitable (*27*): It may thrive in industries with wide variation in consumer valuation for services, where personalized services can be supplied with low marginal costs, and where repeated purchases are likely.

So much for the factors that make privacy intrusions more likely. What factors make them less so? Campbell *et al*. found that the stock price of companies reporting a security breach is more likely to fall if the breach leaked confidential information (*28*). Acquisti *et al*. conducted a similar analysis for privacy breaches (*29*). Their initial results are less conclusive but still point to a negative impact on stock price, followed by an eventual recovery.

Incentives also affect the detailed design of privacy technology. Anonymity systems depend heavily on network externalities: Additional users provide cover traffic necessary to hide users' activities from an observer. This fact has been recognized by some developers of anonymity systems (*30*). As a result, some successful applications such as Tor (*31*), which anonymizes Web traffic, emphasize usability to increase adoption rates.

On the Horizon: Network Topology and Information Security

The topology of complex networks is an emerging tool for analyzing information security. Computer networks from the Internet to decentralized peer-to-peer networks are complex but emerge from ad hoc interactions of many entities using simple ground rules. This emergent complexity, coupled with heterogeneity, is similar to social networks and even to the metabolic pathways in living organisms. Recently a discipline of network analysis has emerged at the boundary between sociology and condensed-matter physics. It takes ideas from other disciplines, such as graph theory, and in turn provides tools for modeling and investigating such networks [see (*32*) for a recent survey]. The interaction of network science with information security provides an interesting bridge to evolutionary game theory, a branch of economics that has been very influential in the study of human and animal behavior.

Network topology can strongly influence conflict dynamics. Often an attacker tries to disconnect a network or increase its diameter by destroying nodes or edges while the defender counters with various resilience mechanisms. Examples include a music industry body attempting to close down a peer-to-peer file-sharing network, a police force trying to decapitate a terrorist organization, and a totalitarian government conducting surveillance on political activists. Police forces have been curious for some years about whether network science might be of practical use in covert conflicts, either to insurgents or to counterinsurgency forces.

Different topologies have different robustness properties with respect to various attacks. Albert *et al*. showed that certain real-world networks with scale-free degree distributions are more robust to random attacks than to targeted attacks (*33*). This is because scale-free networks, like many real-world networks, get much of their connectivity from a minority of nodes that have a high vertex order. This resilience makes them highly robust against random upsets, but if the "kingpin" nodes are removed, connectivity collapses.

The static case of this model is exemplified by a police force that becomes aware of a criminal or terrorist network and sets out to disrupt it by finding and arresting its key people. Nagaraja and Anderson recently extended the model to the dynamic case (*34*), in which the attacker can remove a certain number of nodes at each round and the defenders then recruit other nodes to replace them. Using multiround simulations to study how attack and defense interact, they found that formation of localized clique structures at key network points worked reasonably well, whereas defenses based on rings did not work well at all. This helps to explain why peer-to-peer systems with ring architectures turned out to be rather fragile—and also why revolutionaries have tended to organize themselves in cells.

Concluding Remarks

Over the past few years, a research program on the economics of security has built many cross-disciplinary links and has produced many useful (and indeed delightful) insights from unexpected places. Many perverse aspects of information security that had long been known to practitioners but were dismissed as "bad weather" have turned out to be quite explicable in terms of the incentives facing individuals and organizations, and in terms of different kinds of market failure.

As for the future, the work of the hundred or so researchers active in this field has started to spill over into two new domains. The first is the economics of security generally, where there is convergence with economists studying topics such as crime and warfare. The causes of insurgency, and tools for understanding and dealing with insurgent networks, are an obvious attractor. The second new domain is the economics of dependability. Why is it, for example, that large IT projects fail? We have much better tools for managing complex projects than we did 30 years ago, yet the same proportion of big projects seem to fail—we just build bigger failures nowadays. This suggests that the causes have as much to do with incentives and organizational behavior as with intrinsic system complexity. And as systems become ever more interconnected, the temptation for system owners to try to dump reliability problems on others will increase. There is thus a search beginning for network protocols and interfaces that are "strategy-proof"—that is, designed so that the incentives of the principals are properly aligned and no one can gain by cheating. Designing bad behavior out of systems at the start is much more attractive than trying to police it afterward.

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10.1126/science.1130992

A Fossil Bee from Early Cretaceous Burmese Amber

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Bees are among the most important insect pollinators (*1*). The origin of bees, with their numerous morphological and behavioral adaptations for pollen collection and transport (*2*), contributed to the rapid diversification of angiosperms in the Early to mid-Cretaceous (*3*). Understanding the role that bee pollination played in angiosperm diversification requires an accurate estimate of bee antiquity as well as an understanding of the early evolutionary history of bees.

We report here fossil evidence of bees in the Early Cretaceous. The fossil bears several derived features of bees as well as morphological structures (e.g., branched hairs) presumed to be associated with pollen collection. The specimen originated from an amber mine in the Hukawng Valley (26°20′N, 96°36′E), Kachin state, northern Myanmar (Burma). Palynomorphs obtained from the amber beds where the fossil originated have been assigned to the Upper Albian [~100 million years ago (Ma)] of the Early Cretaceous (*4*). The male holotype is deposited in the Poinar amber collection (accession no. B-Hy-7) maintained at the Oregon State University Insect Collection.

Superfamily Apoidea

Melittosphecidae new family

Type genus: *Melittosphex*

Type species: *Melittosphex burmensis*

Melittosphex burmensis new species

The male specimen of *Melittosphex burmensis* measures 2.95 mm in length (Fig. 1B) and bears branched, plumose hairs on the undamaged portions of the thorax, legs, abdomen, and head (Fig. 1, A and D). The heart-shaped head (0.24 mm in length) bears antennae that originate low on the face [below the midline (Fig. 1A)]. Each antenna bears 11 flagellomeres, establishing that this is a male. The mandibles are elongate and acutely tridentate (Fig. 1, A and C).

The mesosoma (1.45 mm in length) is partially compressed, but the legs and wings are clearly visible. The propodeum bears two distinct posterolateral tubercles (Fig. 1, A and B) with scattered branched hairs. The forewing venation is typical of many small bees, with a distinct stigma, two submarginal cells, and a weakly arcuate basal vein (Fig. 1A), and is unlike that of any extant or fossil apoid wasps. The hindwing is not visible. The hind leg has an elongate, slender hind tibia [lacking distinct tibial spines characteristic of apoid wasps (Fig. 1A)], a narrow hind basitarsus [a characteristic of apoid wasps (Fig. 1A)], and a weakly developed basitibial plate. The hindleg strigil is absent (Fig. 1A). There are two hind-tibial spurs [as in most bees (*1*)]. The midtibia bears two spurs [a groundplan feature of apoid wasps (*1*) (Fig. 1A)]. The male specimen bears several pollen grains between the hairs on the first and second metatarsal segments and adjacent to the antennal cleaner on the left foretarsus.

The metasoma (1.26 mm in length) is slightly compressed, but T7 (the last visible metasomal tergum in males) is undamaged (Fig. 1B). The specimen bears a well-developed pygidial plate (Fig. 1A) on T7, a character that unites bees with crabronid wasps (*5*). Cerci are absent.

Analysis of available morphological data indicates that *Melittosphex* represents an extinct lineage of pollen-collecting Apoidea sister to the modern bees [Supporting Online Material (SOM) text].

M. burmensis establishes that many traits of extant bees were present by ~100 Ma, near the time of the origin of the eudicots [120 to 125 Ma (*3*)]. Other known bee fossils are 35 to 45 million years younger. The small size of *Melittosphex* indicates that at least some of the earliest bees were minute. This is consistent with the small sizes reported for some Early Cretaceous flowers (*6*). Several extant lineages of bees include small species (~3 mm in length), including Colletidae (some Euryglossinae), Halictidae (Nomioidinae), Andrenidae (some Panurginae), and Apidae (Meliponini and Neolarrini) (*1*). *M. burmensis* exhibits traits unique to bees (branched hairs, absence of hind-leg strigil, and absence of hind-tibial spines) as well as groundplan features of apoid wasps (paired mid-tibial spurs and slender hind basitarsus). This mosaic of wasp and bee traits is to be expected from an early, transitional form that bridges the gap between extant bees and crabronid wasps.

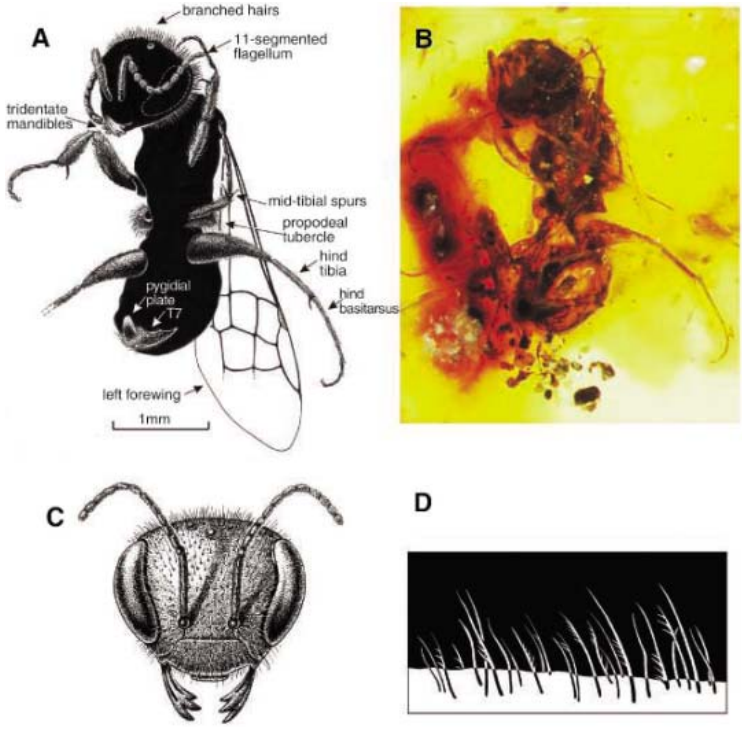

Fig. 1. *Melittosphex burmensis*. (**A**) Ventral view of fossil with key features labeled. (**B**) Photograph of fossil as seen in ventral view. (**C**) Reconstruction of head based on details visible in fossil and information from modern bees. (**D**) Morphology of branched hairs on the hind femur.

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7. We thank M. Prentice and M. Burgett for discussions and A. Boucot, R. Poinar, E. Almeida, S. Cardinal, C. Michener, and J. Liebherr for comments. This project was partially supported by an NSF Research Grant in Systematic Biology to B.N.D. (DEB-0412176). F. Fawcett prepared the illustrations.

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5799/614/DC1
SOM Text
Fig. S1
References

21 August 2006; accepted 2 October 2006
10.1126/science.1134103

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BK_{Ca}-Cav Channel Complexes Mediate Rapid and Localized Ca^{2+}-Activated K^+ Signaling

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Large-conductance calcium- and voltage-activated potassium channels (BK_{Ca}) are dually activated by membrane depolarization and elevation of cytosolic calcium ions (Ca^{2+}). Under normal cellular conditions, BK_{Ca} channel activation requires Ca^{2+} concentrations that typically occur in close proximity to Ca^{2+} sources. We show that BK_{Ca} channels affinity-purified from rat brain are assembled into macromolecular complexes with the voltage-gated calcium channels Cav1.2 (L-type), Cav2.1 (P/Q-type), and Cav2.2 (N-type). Heterologously expressed BK_{Ca}-Cav complexes reconstitute a functional "Ca^{2+} nanodomain" where Ca^{2+} influx through the Cav channel activates BK_{Ca} in the physiological voltage range with submillisecond kinetics. Complex formation with distinct Cav channels enables BK_{Ca}-mediated membrane hyperpolarization that controls neuronal firing pattern and release of hormones and transmitters in the central nervous system.

Large-conductance Ca^{2+}- and voltage-activated K^+ channels (BK_{Ca} or $K_{Ca}1.1$) are fundamental modulators of neuronal signaling (*1*, *2*) by contributing to action potential repolarization (*3*, *4*), mediating the fast phase of afterhyperpolarization (*3*, *5*–*8*), controlling dendritic Ca^{2+} spikes (*9*), and establishing a feedback loop between membrane potential and cytosolic Ca^{2+} that regulates release of hormones and transmitters (*10*–*13*).

The physiological functions of BK_{Ca} channels arise from their unique allosteric activation by two distinct stimuli, membrane depolarization and cytosolic Ca^{2+} ions (*14*–*16*). Increasing Ca^{2+} concentrations ($[Ca^{2+}]_i$) shift the depolarization required for channel opening into the physiological voltage range. In fact, $[Ca^{2+}]_i$ of ≥ 10 μM are usually required for activating BK_{Ca} channels at membrane potentials around 0 mV (*17*). In central nervous system (CNS) neurons, such high levels of $[Ca^{2+}]_i$ are tightly restricted in time and space to local "Ca^{2+}-signaling domains" centered around voltage-activated Ca^{2+} (Cav) channels (*18*, *19*). In these domains, speed and magnitude of Ca^{2+} signals are inversely related to the distance from the Ca^{2+} source and are assessed experimentally by the distinct properties of the Ca^{2+} chelators EGTA and BAPTA. Thus, Ca^{2+}-sensitive processes affected by millimolar concentrations of BAPTA but not EGTA are assumed to be placed within ~20 nm from the Cav channels (nanodomain), while processes with an equal BAPTA/EGTA sensitivity are located between 20 and 200 nm (microdomain) or even further away from the Ca^{2+} source (*18*).

Functional characterization in various types of neurons provided two hallmarks for the activation of BK_{Ca} under normal conditions. First, BK_{Ca} channels reside in close spatial proximity to Cav channels, as they were robustly activated by Ca^{2+} influx through the Cav channels in the presence of EGTA, whereas BAPTA at millimolar concentrations largely attenuated or abolished the functional channel-channel coupling (*3*, *13*, *20*–*22*). Second, BK_{Ca} channels appear to be selectively activated by a subset of Cav channels with distinct functional properties and subcellular distribution. Thus, P/Q-, N- and L-type Cav channels activate BK_{Ca} either selectively or concertedly in nerve terminals, dendrites, or somata of various types of CNS neurons (*3*, *6*, *13*, *20*, *23*, *24*).

Despite its fundamental importance for the physiology of BK_{Ca} channels, the mechanism underlying the intimate and selective association between BK_{Ca} and Cav channels is as yet unknown, and selective coupling between BK_{Ca} and Cav channels in heterologous expression systems has not been demonstrated.

Affinity Purification of BK_{Ca} Channel Complexes from Rat Brain

We used affinity purifications (AP) with two different $BK_{Ca}\alpha$ subunit-specific antibodies (anti-BKα and anti-BKα* Abs) on solubilized plasma membrane–enriched protein fractions prepared from total rat brain (*25*). Separation by blue native and subsequent denaturing gel electrophoresis showed that these protein fractions contained high-molecular-weight complexes of BK_{Ca} channels [Fig. 1A, (*26*)]. Total eluates obtained in APs with the two anti-BKα Abs and with several immunoglobulin G (IgG) pools (preimmunization IgGs and antibodies unrelated to BKα) serving as a control were subjected to analysis by nanoflow liquid chromatography tandem mass spectrometry (nano-LC MS/MS) (Fig. 1A). This approach identified the α subunit of BK_{Ca} channels (BKα) by retrieving ≥ 66 different peptide fragments (for each anti-BKα Ab) covering ~75% of the BKα primary sequence (Fig. 1, B and C and Table 1, top). In addition, MS/MS spectra from the anti-BKα eluates unambiguously identified the two BKβ subunits (BKβ2 and BKβ4) expressed in the CNS (*17*), as well as several Cav channel α and β subunits (Table 1, top). The Cavα subunits specifically retained by both anti-BKα Abs were Cav1.2, Cav2.1 and Cav2.2 (Table 1 and fig. S1) (*26*) encoding the pore-forming subunits of the L-, P/Q- and N-type Cav channels, respectively (*27*). In fact, Cav2.1 was the protein most abundantly copurified with BKα; all together, MS/MS analyses detected 43 different peptides covering ~44% of the Cav2.1 amino acid sequence. Similar sequence coverage was obtained for the specifically copurified Cavβ subunits Cavβ1b, Cavβ2, and Cavβ3 (Table 1 and fig. S1). In contrast, Cav2.3, R-type Cav channels (*27*), and the Cavβ4 subunit were detected in the eluates from both anti-BKα Abs and control IgGs with similar abundance (Table 1 and fig. S1).

Coassembly with Cav1.2 channels was confirmed by subsequent reverse purification using an antibody specific for the Cav1.2 subunit (anti-Cav1.2) and suitable for AP from rat brain plasma membranes. As illustrated in Fig. 2A by the ion chromatogram (left) and the MS/MS spectrum (right) of one out of the eight unique peptides obtained, BKα was copurified by anti-Cav1.2 but not by the control IgG pools (Table 1, bottom).

Coassembly of Heterologously Expressed BK_{Ca} and Cav Channels

The copurification of BK_{Ca} with specific Cav channel subtypes from rat brain plasma membranes was reproduced by APs from culture cells that heterologously expressed BK_{Ca} channels and either Cav1.2 or Cav2.1 channels. For these experiments, the respective channel subunits BKα and BKβ4, as well as Cav1.2 or Cav2.1, Cavβ1b or Cavβ3, and α2δ (*28*), were transfected into culture cells or injected as cRNAs into *Xenopus* oocytes (*26*). Figure 2B and fig. S2A illustrate the results of coimmunoprecipitations using anti-BKα and anti-Cav1.2 on the BK_{Ca}-Cav1.2 coexpressions in culture cells. Thus, anti-BKα effectively and specifically retained the Cav1.2 subunit, and anti-Cav1.2 coprecipitated the BKα subunit with similar efficiency. An equivalent result was obtained from an AP using anti-BKα on *Xenopus* oocytes coexpressing BK_{Ca} and Cav2.1 channels. In this experiment, copurification of the Cav

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channel was verified by MS/MS analysis that retrieved 31 peptides for BKα and 9 and 11 peptides specific for the Cav2.1 and Cavβ3 subunits, respectively (fig. S2B).

Functional Characteristics of BK_{Ca}-Cav Complexes

Next, the functional properties of BK_{Ca}-Cav2.1 channel complexes were investigated in giant inside-out patches (*26*) excised from *Xenopus* oocytes coexpressing BK_{Ca} (BKα and BKβ4) and run-down deprived Cav2.1 channels [Cav2.1(I1520H), Cavβ3, and α2δ (*29*)]. Figure 3A shows typical current traces recorded in response to step depolarizations in the physiological voltage range. Thus, for voltage steps above the activation threshold of Cav2.1 channels, current responses were biphasic (in all 135 patches tested): an initial Ca^{2+} inward current that was followed by an outward K^+ current, as would be expected for activation of BK_{Ca} channels by influx of Ca^{2+} ions through the Cav2.1 channels (Fig. 3A). The coupling between both channels was mandatory for activation of BK_{Ca} in the physiological voltage range as shown by control experiments lacking expression of the Cav channels (Fig. 3B). The time course of the Cav2.1-BK_{Ca} coupling reflected by the interval between the onsets of Ca^{2+} and K^+ currents (*26*) was voltage-dependent and markedly reduced by membrane depolarization. At potentials positive to 0 mV, this time interval was less than one millisecond (Fig. 3A, inset); mean values for the duration ($n = 15$ experiments) were 0.75 ± 0.24 ms (at 20 mV) and 0.95 ± 0.18 ms (at 10 mV). The amplitude of the Cav channel–activated BK_{Ca} current was strongly voltage-dependent and exhibited a bell-shaped steady-state current-voltage (*I-V*) relation with a peak amplitude at about 20 mV (Fig. 3B). Both the shape of the *I-V* relation and the time course of the Cav2.1-BK_{Ca} coupling are a reflection of several factors, including the voltage-dependent gating properties of Cav2.1 (Fig. 3C and fig. S3A) and BK_{Ca} channels, the amplitude of the Ca^{2+} current (Fig. 3C), and the Ca^{2+} sensitivity of BK_{Ca} channels (Fig. 3D). In particular, increase in open probability and faster activation kinetics of the Cav channels promote accelerated coupling (Fig. 3A) and increase in the BK_{Ca} currents (Fig. 3B), whereas the decrease in Ca^{2+} current amplitude (due to a reduced driving force at voltages approaching the Ca^{2+} reversal potential) leads to reduction and cessation of BK_{Ca} currents at voltages >20 mV (Fig. 3B). Similar results for coupling and *I-V* relation were obtained with Cav2.2 (Cav2.2α, Cavβ3, and α2δ) channels (fig. S3B).

Comparison of BK_{Ca} currents evoked by Cav2.1 and those recorded in excised patches from oocytes expressing only BK_{Ca} with defined $[Ca^{2+}]_i$ (*26*) was used to estimate the Ca^{2+} concentration delivered to BK_{Ca} via the Cav channels. The robust BK_{Ca} activity observed at membrane potentials ≤0 mV (Fig. 3B) suggested that Cav2.1 channels might provide Ca^{2+} concentrations of ≥10 μM (Fig. 3D). This value was confirmed by the time constants obtained from monoexponential fits to the activation time course ($\tau_{activation}$) of BK_{Ca} currents. The values determined for $\tau_{activation}$ of Cav2.1-evoked BK_{Ca} currents were similar to the results obtained from BK_{Ca} currents at a $[Ca^{2+}]_i$ of 10 μM across the entire voltage range tested (Fig. 4A).

The BK_{Ca}-Cav2.1 coupling was further probed for its sensitivity to Ca^{2+}-buffers. Excised patches were successively perfused with intracellular solutions containing EGTA and BAPTA in 5 mM

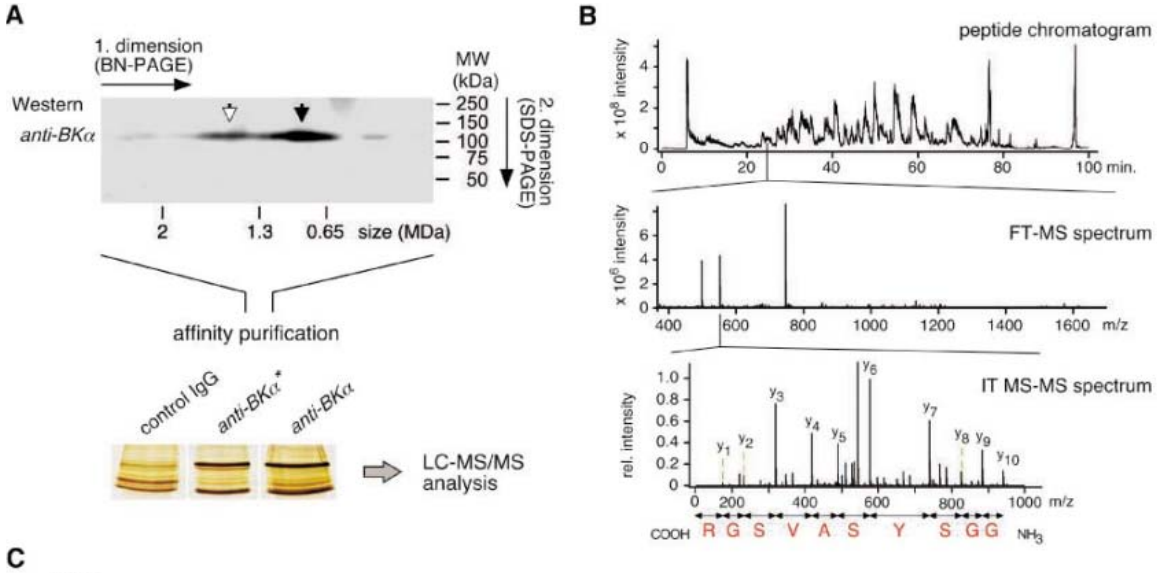

Fig. 1. Affinity purification of BK_{Ca} channel complexes from CNS plasma membranes. (**A**) (Top) High-molecular-weight complexes of BK_{Ca} channels in solubilized plasma membrane–enriched protein fractions from rat brain visualized by two-dimensional gel electrophoresis (*26*). Solubilized protein complexes were separated by blue native polyacrylamide gel electrophoresis (BN-PAGE, 1. dimension) and denaturing SDS-PAGE (2. dimension), and were subsequently Western-probed with anti-BKα (*42*). BK_{Ca} channels (4BKα + 4BKβ) indicated by filled arrowhead, main fraction of high-molecular weight complexes of BK_{Ca} channels denoted by open arrowhead. (Bottom) Eluates of APs with two different anti-BKα Abs (anti-BKα and anti-BKα*) or a pool of pre-immunization IgGs. Total eluates were shortly run into a SDS-gel, in-gel trypsinized, and analyzed by nano-LC MS/MS spectrometry. (**B**) (Top) High-performance liquid chromatography (HPLC) chromatogram of peptides obtained by trypsinization of anti-BKα eluates in the mass range of 50 to 150 kD. (Middle and bottom) MS and MS/MS spectra of a peptide unique for BKα. The peptide had a mass/charge (*m/z*) ratio of 552.76154 and was eluted at the time point indicated. In the MS/MS spectrum, the complete y^+-ion series is indicated, and the amino acid sequence derived from the mass differences is given in carboxy-to-amino-terminal direction. (**C**) Coverage of the BKα amino acid sequence by the peptides identified with nano-LC MS/MS. Peptides identified by mass spectrometry are in red, those accessible to but not identified in MS/MS analyses are in black, and peptides not accessible to the MS/MS analyses used are in gray. Lines denote hydrophobic segments S0 to S10; the blue box highlights the BKα peptide shown in (B).

and 10 mM concentration. Cav channel–activated BK_{Ca} currents (at 20 mV) were unaffected by 10 mM EGTA (with respect to the standard 5 mM EGTA), whereas 5 mM and 10 mM BAPTA reduced their amplitude to 28 ± 5% (mean ± SD of 9 patches) and 10 ± 4%, respectively (Fig. 4B). This reduction resulted from a decreased $[Ca^{2+}]_i$ at the BK_{Ca} channels, as indicated by their markedly slowed activation time course (Fig. 4B, inset, and fig. S3C). The $\tau_{activation}$ values determined for a membrane potential of 20 mV were 13.4 ± 2.1 ms (mean ± SD, $n = 9$) and 19.9 ± 2.1 ms ($n = 9$) for 5 mM and 10 mM BAPTA, whereas in EGTA the respective value was 6.9 ± 1.1 ms ($n = 12$; all values were significantly different from each other, with $P < 0.0005$, pairwise Student's t test). Other properties of Cav2.1-activated BK_{Ca} currents, including the bell-shaped steady-state I-V, were similar in BAPTA- and EGTA-buffered intracellular solutions (fig. S3).

The distinct effects of EGTA and BAPTA on the Cav-activated BK_{Ca} currents place the channels within a "local nonequilibrium Ca^{2+} domain," a steep Ca^{2+} concentration gradient around a Cav channel that rapidly builds up after opening of the channel pore in the presence of mobile buffers (*18*, *19*). Figure 4C depicts such Ca^{2+} concentration profiles simulated for a Cav channel with a single-channel conductance of 1.7 pS [(*30*), for 1.3 mM external Ca^{2+}] and EGTA or BAPTA at concentrations of 5 mM and 10 mM. Accordingly, the distance between BK_{Ca} and Cav2.1 channels fitting the data on both amplitude and activation time course of BK_{Ca} currents may be estimated to ~10 to 15 nm.

Specificity of BK_{Ca}-Cav Channel Complex Formation

Cav1.2, Cav2.1, and Cav2.2 were specifically copurified with BK_{Ca} channels from rat brain, whereas Cav2.3 was not (Table 1 and fig. S1). We, therefore, investigated the specificity of BK_{Ca}-Cav coassembly using coexpression of either Cav1.2 or Cav2.3 (plus Cavβ1b and α2δ) with BK_{Ca} (BKα and BKβ4) in Chinese hamster ovary (CHO) cells. For functional recordings, the patch-clamp technique was used in whole-cell configuration (*26*). Figure 5A shows representative current responses to depolarizing voltage steps recorded from coexpression of BK_{Ca} with either of the two Cav subtypes after equilibration of the intracellular milieu with the pipette solution. As indicated by the biphasic current response and the bell-shaped I-V relation, Cav1.2 channels effectively activated the coexpressed BK_{Ca} channels [Fig. 5, A (top) and B] (n of 48 cells), similar to the Cav2.1-BK_{Ca} coexpression in oocytes. Again, the Ca^{2+} provided through the Cav channels was mandatory for the BK_{Ca} currents as reflected by their complete decay paralleling the pronounced inactivation of the Cav1.2 channels (Fig. 5A and fig. S4A). The Cav1.2-BK_{Ca} coupling could not be disrupted with EGTA but was reversibly disrupted after replacing EGTA in the pipette solution with BAPTA ($n = 13$ cells) (fig. S4C).

In marked contrast to Cav1.2, Cav2.3 channels failed to promote activity of the coexpressed BK_{Ca} channels under standard conditions ($n = 9$ cells) (Fig. 5, A and B). This failure was not due to an inefficient expression of BK_{Ca} but rather resulted from equilibration of the cytoplasm with EGTA as monitored in a series of experiments applying step-depolarizations every 30 to 45 s (Fig. 5C, D). Thus, immediately after establishing whole-cell configuration, Ca^{2+} influx through Cav2.3 channels elicited robust BK_{Ca} currents that vanished over the following 3-min period required for diffusion of EGTA into the CHO cell (Fig. 5D) ($n = 8$ cells). The Ca^{2+} currents through Cav2.3 channels were unaffected by EGTA (Fig. 5A and fig. S4B), as were both the Ca^{2+} and K^+ currents in the Cav1.2-BK_{Ca} coexpressions used as a control ($n = 16$ cells) (Fig. 5A). In line with the distinct effect of EGTA, immunoprecipitation with the anti-BKα Ab failed to copurify the Cav2.3 protein from Cav2.3-BK_{Ca} coexpressing cells (Fig. 5D).

The molecular basis of this subtype specificity is encoded by the pore-forming α subunits. Thus, when cells coexpressing BKα and Cav1.2α in the absence of the respective auxiliary subunits were used for coimmunoprecipitation, both the anti-BKα and the anti-Cav1.2 Abs effectively purified both channel α subunits (Fig. 5E), although to a somewhat lesser extent compared to the previous experiment with cells expressing all BK_{Ca} and Cav channel subunits (Fig. 2).

Properties of "Native" BK_{Ca}-Cav Channel Complexes

Finally, the functional properties obtained for heterologously reconstituted BK_{Ca}-Cav channel complexes were compared to those of their native counterparts. We used chromaffin cells as a model system because of their well-known coupling between Q- and L-type Cav and BK_{Ca} channels (*31*) and their suitability for electrophysiology and efficient intracellular dialysis.

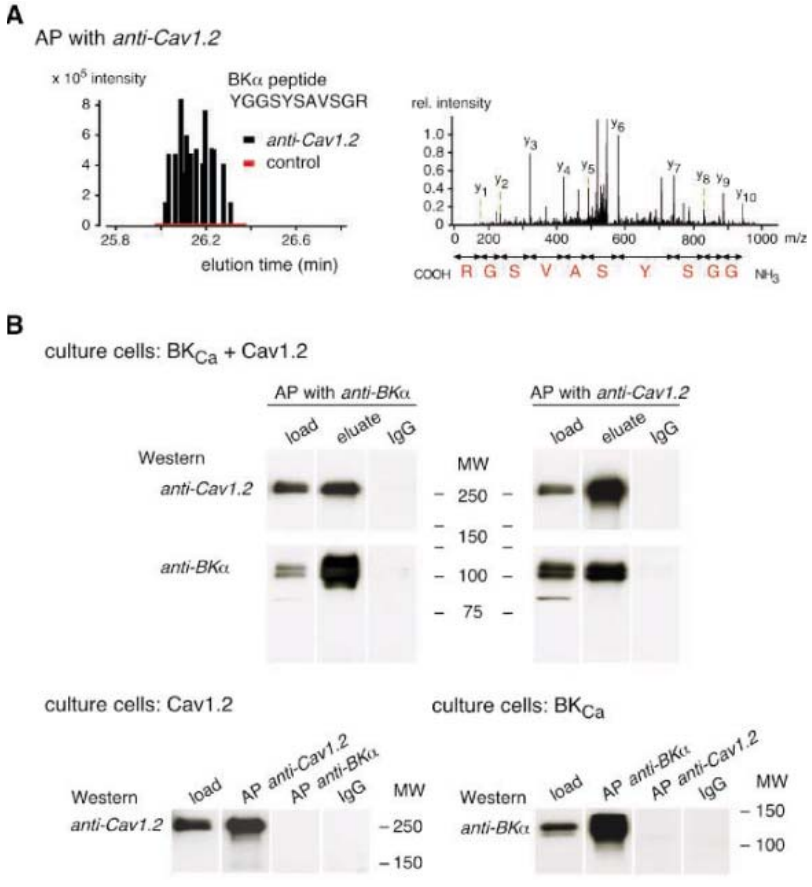

Fig. 2. Co-assembly of BK_{Ca} and Cav channels in the CNS and heterologous expression systems. (**A**) Identification of BK_{Ca} in an AP from CNS plasma membranes with anti-Cav1.2. Ion chromatogram (left panel, reflecting the signal generated by the m/z ratio of 552.76154 in the mass spectrometer during elution from the HPLC) and corresponding MS/MS-spectrum (right panel) of one of the eight BKα-specific peptides obtained (the same peptide as in Fig. 1B). The m/z ratio of 552.76154 (±10 parts per million) was not detected in elutions from APs with preimmunization IgG pools serving as a control. (**B**) Copurification of BK_{Ca} and Cav channels from culture cells expressing BK_{Ca} (BKα and BKβ4) and Cav1.2 (Cav1.2α, Cavβ1b, and α2δ) channels. Eluates from APs with anti-BKα (left) or anti-Cav1.2 (right) Abs were separated by SDS-PAGE and Western-probed as indicated. Specificity of APs with anti-BKα and anti-Cav1.2 were verified in purifications with cells expressing Cav1.2 (left) or BK_{Ca} (right) channels alone.

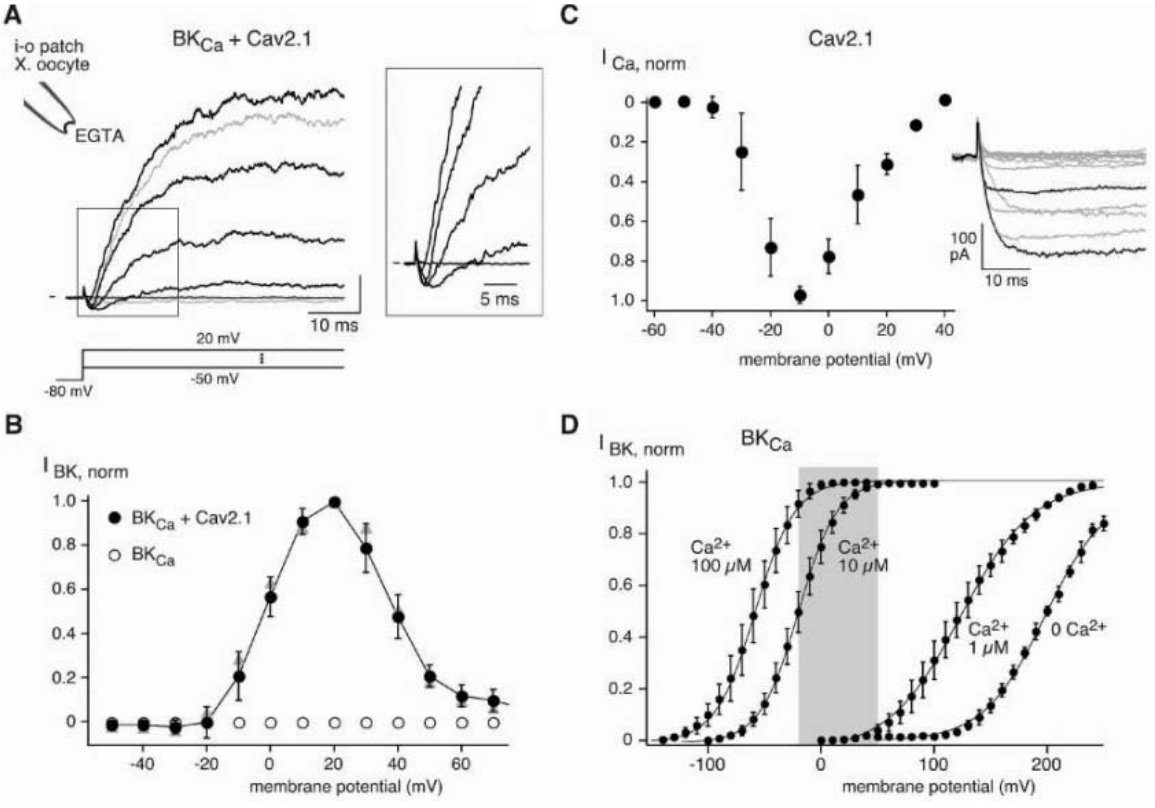

Fig. 3. Functional coupling of heterologously expressed BK_{Ca} and Cav2.1 channels. (**A**) Current response to the indicated voltage steps (–50 to 20 mV at 10 mV increments, holding –80 mV) recorded under physiological ion conditions (1.3 mM extracellular Ca^{2+}) in a giant inside-out (i-o) patch excised from an oocyte coexpressing BK_{Ca} (BKα and BKβ4) and Cav2.1 [Cav2.1(I1520H), Cavβ3, and α2δ] channels. Cytoplasmic solution was buffered with 5 mM EGTA. Current scale is 1 nA. (Inset) Current traces in black (–50, –20, –10, 0, and 20 mV) at expanded time scale. (**B**) Normalized (outward) currents through BK_{Ca} channels as a function of membrane potential recorded in excised i-o patches from oocytes expressing BK_{Ca} and Cav2.1 channels (filled symbols) or BK_{Ca} channels alone (open symbols). Data points are mean ± SD of 10 experiments [gray triangles are from the experiment in (A)]. (**C**) Ca^{2+} (inward) currents normalized to maximum and recorded under conditions as in (A) in excised i-o patches from oocytes expressing Cav2.1 channels as in (A). (Inset) Representative experiment, traces at –10 and 20 mV are in black. (**D**) Steady-state activation curves of BK_{Ca} channels recorded at the $[Ca^{2+}]_i$ indicated in giant i-o patches from oocytes. Data points are mean ± SD of 6 experiments. Gray bar denotes the voltage range of BK_{Ca} channel activation by coexpressed Cav2.1 channels from (A) and (B). Continuous lines are fits of Boltzmann functions to the data with values for $V_{½}$ and slope factor of 197.8 mV and 27.1 mV (0 $[Ca^{2+}]_i$), 123.2 mV and 32.1 mV (1 μM $[Ca^{2+}]_i$), –19.9 mV and 17.1 mV (10 μM $[Ca^{2+}]_i$), and –58.1 mV and 17.5 mV (100 μM $[Ca^{2+}]_i$).

Figure 6A shows a typical sequence of Cav-mediated inward and BK_{Ca}-mediated outward currents recorded in response to a step-depolarization in the presence of 5 mM EGTA (n = 32 cells). Coupling of the tetraethylammonium (TEA)–sensitive BK_{Ca} currents to the Ca^{2+} influx is indicated by their deactivation after interruption of the Ca^{2+} influx by a voltage step to the Ca^{2+} reversal potential (Fig. 6A) (*31*). In addition, BK_{Ca} currents could be eliminated by application of nifedipine and ω-agatoxin IVA, specific blockers of Cav1.2 and Cav2.1 that are expressed in chromaffin cells (Fig. 6B). The spatiotemporal dynamics of the Cav-BK_{Ca} coupling was probed by replacing EGTA in the recording pipette with 5 mM BAPTA. The respective current transients exhibited similar overall properties as with EGTA, although the amplitude of the BK_{Ca} currents was decreased by roughly 80% (ratio of mean currents), and the deactivation at the Ca^{2+} reversal potential was markedly accelerated, as expected for a lower $[Ca^{2+}]_i$ at the BK_{Ca} channels (Fig. 6A).

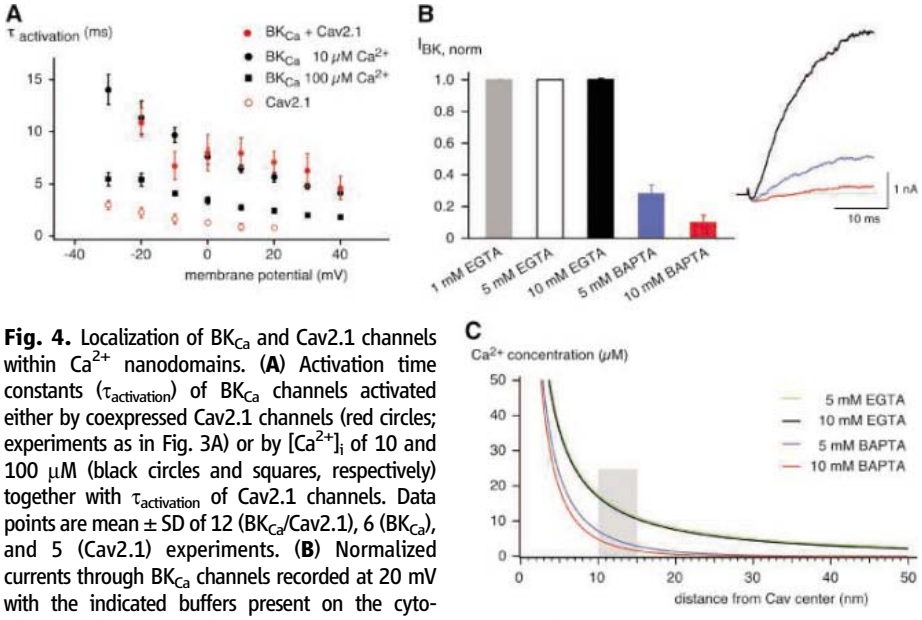

Fig. 4. Localization of BK_{Ca} and Cav2.1 channels within Ca^{2+} nanodomains. (**A**) Activation time constants ($\tau_{activation}$) of BK_{Ca} channels activated either by coexpressed Cav2.1 channels (red circles; experiments as in Fig. 3A) or by $[Ca^{2+}]_i$ of 10 and 100 μM (black circles and squares, respectively) together with $\tau_{activation}$ of Cav2.1 channels. Data points are mean ± SD of 12 (BK_{Ca}/Cav2.1), 6 (BK_{Ca}), and 5 (Cav2.1) experiments. (**B**) Normalized currents through BK_{Ca} channels recorded at 20 mV with the indicated buffers present on the cytoplasmic side of i-o patches from oocytes coexpressing BK_{Ca} and Cav2.1. Data points are mean ± SD of 9 experiments. (Inset) Representative current traces with 10 mM EGTA (black), 5 mM BAPTA (blue), or 10 mM BAPTA (red). (**C**) Steady-state Ca^{2+} concentration profiles at the cytoplasmic opening of a single Cav channel. The profiles were determined with the CalC software v. 5.4.0 (*43*) (single channel conductance of 1.7 pS, driving force of 60 mV). The gray bar represents the range fitting the experimental data shown in Figs. 3 and 4.

Discussion

The central finding of this work is that two distinct classes of ion channels, BK-type Ca^{2+}-activated K^+ channels and voltage-gated Ca^{2+}

channels, may be assembled into macromolecular channel-channel complexes in the CNS. Functionally, these complexes reconstitute Ca^{2+} nanodomains, where Ca^{2+} influx through the Cav channels provides the $[Ca^{2+}]_i$ required for rapid and robust activation of BK_{Ca} channels in the physiologically relevant voltage range.

Formation of BK_{Ca}-Cav channel complexes. For characterization of the molecular environment of BK_{Ca} channels, we started out from proteomic analysis combining APs of appropriately solubilized proteins with nano-LC MS/MS analysis of total eluates. When applied to plasma membrane preparations from total rat brain (*25*), this approach isolated BK_{Ca} channels with high efficiency and provided information on the BKα protein [sequence coverage of ~75%, splice variations] and on proteins associated with BK_{Ca} channels. Respective analyses by nano-LC MS/MS revealed two striking results with respect to the mechanism of native BK_{Ca} channel activation. First, the proteins most efficiently copurified with BKα were members of the Cav-channel family (Table 1), with particular abundance of Cav2.1. Second, proteins with a similar peptide yield and proposed scaffolding function were not identified, nor did mass spectrometry retrieve molecules

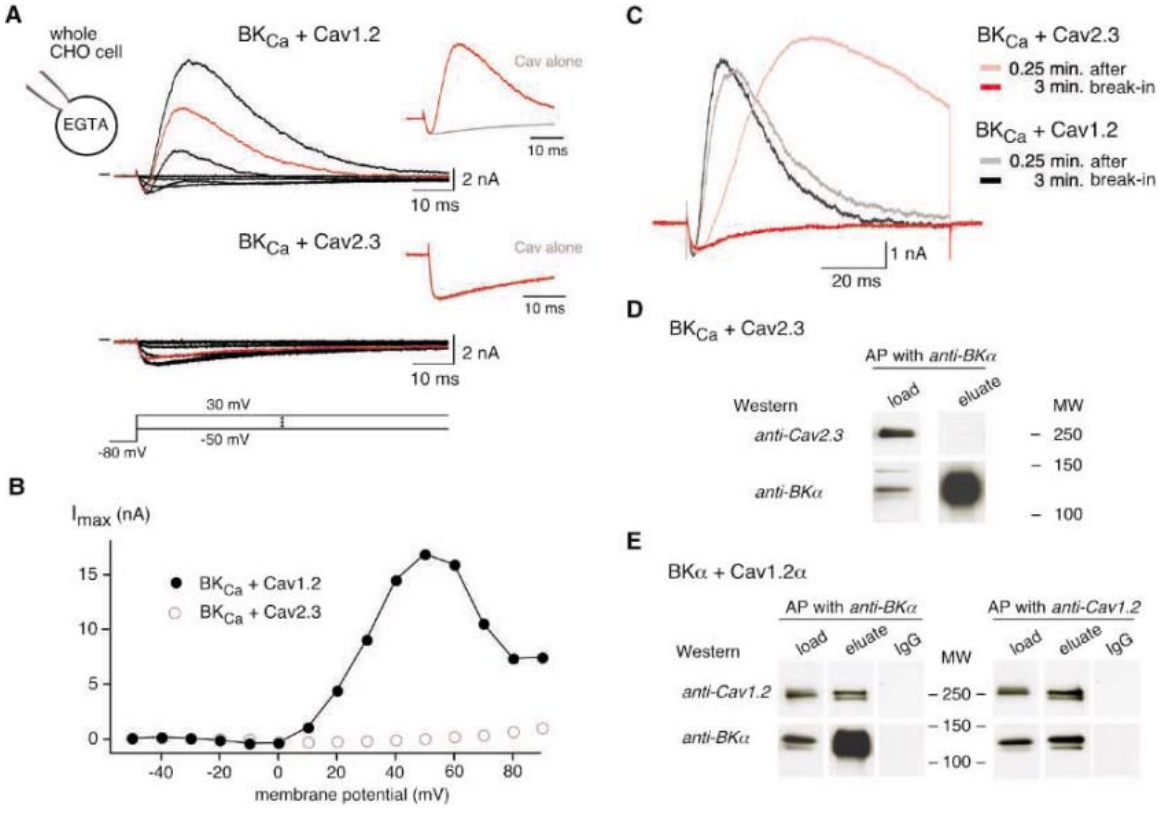

Fig. 5. BK_{Ca}-Cav coassembly is subtype-specific and determined by the α subunits. (**A**) Current response to the indicated voltage steps (−50 to 30 mV at 10 mV increments) recorded under physiological ion conditions in whole CHO cells coexpressing BK_{Ca} (BKα and BKβ4) and either Cav1.2 (top) or Cav2.3 (bottom) channels. Cav channels were assembled from Cav1.2α/Cav2.3α, Cavβ1b, and α2δ. Traces recorded upon a voltage step to 20 mV are highlighted in red and superimposed in the inset with the response of the respective Cav subtype to the same voltage step. Time constants (mean ± SD) for the decay of BK_{Ca} and Cav1.2 currents obtained from monoexponential fits were 28.4 ± 9.9 ms and 27.6 ± 11.7 ms, respectively. (**B**) *I-V* relation of the experiments in (A); symbols as indicated. (**C**) Activation of BK_{Ca} by Cav2.3 channels is abolished by 5 mM EGTA washed into CHO cells after establishing whole-cell configuration. Current responses recorded upon voltage steps to 30 mV 0.25 min (light) and 3 min (dark) after whole-cell break-in into cells coexpressing BK_{Ca} channels with either Cav2.3 (red) or Cav1.2 (black) channels. (**D**) Failure of anti-BKα to purify the Cav2.3α subunit from culture cells coexpressing BK_{Ca} (BKα and BKβ4) and Cav2.3 channels (Cav2.3α, Cavβ1b, and α2δ). Load and anti-BKα eluate were separated by SDS-PAGE and Western-probed by anti-BKα and an antibody against the Cav2.3α subunit (anti-Cav2.3). (**E**) Copurification of BK_{Ca} and Cav channel α subunits from culture cells expressing BKα and Cav1.2α. Eluates from APs with anti-BKα (left) and anti-Cav1.2 (right) Abs were separated by SDS-PAGE and Western-probed as indicated.

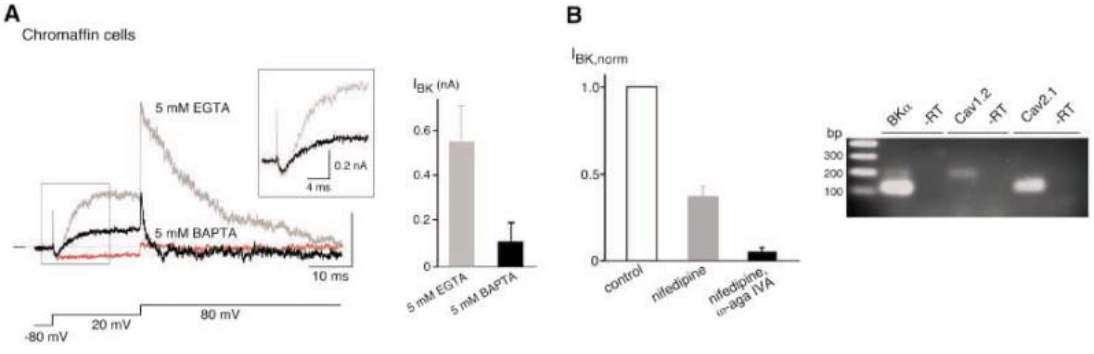

Fig. 6. Recombinant BK_{Ca}-Cav channel complexes match the characteristics of their native counterparts. (**A**) (Left) Current responses to the indicated voltage protocol [adapted from (*22*)] recorded in chromaffin cells with either 5 mM EGTA (gray) or 5 mM BAPTA (black) in the whole-cell pipette; the trace in red shows block of the BK_{Ca} current by 5 mM extracellular TEA (at 5 mM intracellular EGTA). Current scale is 0.5 nA. (Inset) Current traces at expanded time scale. (Right) Mean ± SD of currents through BK_{Ca} channels ($n = 5$) from experiments as on the left. (**B**) Identification of L-type (Cav1.2) and P/Q-type (Cav2.1) channels as the Cav channels coupling to BK_{Ca} channels in chromaffin cells. (Left) Mean ± SD of BK_{Ca}-mediated currents ($n = 5$) before and after addition of the L-type Cav channel blocker nifedipine (5 μM) and the P/Q-type channel blocker ω-agatoxin IVA (1 μM). (Right) PCR amplification of transcripts coding for BKα and the Cavα subunits indicated from chromaffin cells; control reactions (without reverse transcription) are referred to as −RT.

suggested to link BK_{Ca} and Cav channels (*32*). For the Cav channel α subunits identified, quantitative comparisons (between eluates of the anti-BKα Abs and control IgGs) indicated specific copurification for Cav1.2, Cav2.1, and Cav2.2, whereas Cav2.3 was dubbed nonspecific by our specificity scores (Table 1 and fig. S1).

Analyses using biochemistry and electrophysiology on heterologously coexpressed Cav and BK_{Ca} channels confirmed the subtype-specific assembly suggested by the proteomic approach. Thus, Cav1.2/Cav2.1 and BK_{Ca} channels were effectively copurified from culture cells and *Xenopus* oocytes without a requirement for additional exogenous partners (Figs. 2 and 5, and fig. S2). The functional properties of the Cav-BK_{Ca} coupling fully matched the criteria of Ca^{2+} nanodomains, with an estimated distance between channels of ~10 nm (*18*) (Fig. 4 and fig. S4), a value very similar to the 9.5 nm recently determined for the diameter of the voltage-gated K^+ channel Kv1.2 in its crystallized form (*33*). Mechanistically, channel-channel assembly appears to be determined by the α subunits of BK_{Ca} and Cav channels, although a ubiquitously expressed partner protein that escaped our MS/MS analyses cannot be completely ruled out.

Relevance of BK_{Ca}-Cav channel complexes. Formation of stable macromolecular complexes with Cav channels affects the physiology of BK_{Ca} channels in several ways. First, complex formation provides a simple molecular solution to the issue of how BK_{Ca} channels may be supplied with micromolar $[Ca^{2+}]_i$ without affecting other Ca^{2+}-dependent metabolic processes. Second, complex formation puts the activity of BK_{Ca} channels under tight control of their Cav partners. In the context of an excitable cell, this tight coupling ensures that activation of BK_{Ca} channels occurs fast enough to shape the action potential by contributing to its repolarization (*4*, *7*, *8*) and to generate the fast afterhyperpolarization following single Na^+ or Ca^{2+} spikes in various types of CNS neurons (*1*, *3*, *6*, *7*, *34*).

BK_{Ca} signaling via coassembled Cav channels will be shaped by the distinct distribution of Cav channels to particular types of cells or subcellular compartments (Table 1) (*35*, *36*). In fact, all Cav channel subtypes identified were found as partners of somatic BK_{Ca} channels in distinct types of CNS neurons (*3*, *6*, *13*, *20*, *23*, *24*, *37*). In their preferred subcellular localization (*38*, *39*), the presynaptic compartment, however, BK_{Ca} channels appear to be fueled by P/Q- and N-type Cav channels (*6*, *40*), in line with our efficient copurification of the Cav subunits Cav2.1 and Cav2.2. Functionally, presynaptic BK_{Ca} channels were shown to control transmitter release by narrowing the action potential and reducing Ca^{2+} influx into the presynaptic elements (*6*, *12*, *40*) and to operate as an "emergency brake" that prevents cell damage in the case of globally increased $[Ca^{2+}]_i$ (*41*). Both functions may be related to the molecular arrangement of BK_{Ca} channels: Control of transmitter release would well fit with the properties of BK_{Ca}-Cav complexes, whereas emergency braking may be attributed to uncomplexed BK_{Ca} channels.

The BK_{Ca}-Cav channel complexes represent a molecular unit providing effective and precisely timed hyperpolarization of the membrane potential in response to local Ca^{2+} influx.

Table 1. (**Top**) BK_{Ca} and Cav channel subunits affinity-purified with anti-BKα from CNS plasma membranes and identified by nano-LC MS/MS. (**Bottom**) BK_{Ca} and Cav channel subunits affinity-purified with anti-Cav1.2 from CNS plasma membranes. Procedures used for affinity-purification and mass spectrometry, as well as the criteria for protein identification, are detailed in (*26*). remSC is relative exponentially modified sequence coverage. rPQ-Score is relative protein query score. Values for remSC > 5 and rPQ-Scores > 4 indicate specific purification by anti-BKα or anti-Cav1.2 over control IgG pools. * indicates lower estimates of the rPQ score with no matching peptide fragments in the controls.

	Protein ID	remSC	rPQ-Score
BK_{Ca} subunits	BKα (K_{Ca}1.1,KCNMA1)	48.1	322.3
	BKβ2 (KCNMB2)	∞	16.0*
	BKβ4 (KCNMB4)	∞	112.0*
Cav subunits	Cav2.1 (α1A)	∞	496.0*
	Cav1.2 (α1C)	∞	40.0*
	Cav2.2 (α1B)	5.5	4.9
	Cav2.3 (α1E)	3.8	2.4
	Cav β1b	∞	124.0*
	Cav β2	∞	100.0*
	Cav β3	6.3	4.1
	Cav β4	2.3	2.5
Cav subunits	Cav1.2 (α1C)	∞	216.0*
	Cav β1b	∞	128.0*
	Cav β2	∞	104.0*
	Cav β3	∞	104.0*
	Cav β4	6.3	5.0*
BK_{Ca} subunits	BKα	∞	24.0*

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44. We thank P. Jonas for insightful discussions and critical reading of the manuscript and J. Yang for the generous gift of the Cav2.1 clones. This work was supported by grants of the Deutsche Forschungsgemeinschaft to B.F. (Fa 332/5-1,2 and GRK843).

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5799/615/DC1
Materials and Methods
Figs. S1 to S4
References

24 July 2006; accepted 22 September 2006
10.1126/science.1132915

Anatomy of a Flaring Proto-Planetary Disk Around a Young Intermediate-Mass Star

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Although planets are being discovered around stars more massive than the Sun, information about the proto-planetary disks where such planets have built up is sparse. We have imaged mid-infrared emission from polycyclic aromatic hydrocarbons at the surface of the disk surrounding the young intermediate-mass star HD 97048 and characterized the disk. The disk is in an early stage of evolution, as indicated by its large content of dust and its hydrostatic flared geometry, indicative of the presence of a large amount of gas that is well mixed with dust and gravitationally stable. The disk is a precursor of debris disks found around more-evolved A stars such as β-Pictoris and provides the rare opportunity to witness the conditions prevailing before (or during) planet formation.

Based on the growing number of known planetary systems (*1*) and on the wealth of observations of disks around young stellar objects (*2*, *3*), it is now well established that planets around main-sequence solar-type stars form in massive, gaseous, and dusty proto-planetary disks that survive for several million years around the nascent stars (*4*). The situation is less clear for stars of more than ≈2 solar masses. Such stars have a much higher luminosity than solar-type stars, and, according to models, processes such as photoevaporation may be at work clearing the inner disk in a few million years (*5*). Whereas radial velocity surveys have just started to reveal planets around stars about twice as massive as the Sun (*6*), current imaging observations of proto-planetary disks around stars with such a mass remain very sparse (*3*). Most resolved disks are debris disks around A-type stars that are on the main sequence (*3*, *7*). In such disks, the gas has been dispersed, and planets have probably formed already, as indicated by asymmetries and ring-like structures in the disks (*4*). The lack of well-resolved images of proto-planetary disks around much younger A stars, still on the pre–main sequence, is due to the fact that such stars are less numerous than their solar-type equivalents, the T-Tauri stars, and in general are located farther away from Earth. As a result, the fallback option to estimate the properties of the disks around these stars has been to fit their spectral energy distribution (SED). By doing so, the pre–main sequence stars of intermediate mass (≈2 to 4 solar masses), the so-called Herbig Ae (HAe) stars, have been classified in two groups: Group I members feature a rising SED in the 10- to 60-micrometer (μm) wavelength range [mid- and far-infrared (IR)], whereas group II members feature a flatter SED (*8*). The preferred physical interpretation is that group I disks are flared and group II disks are geometrically flatter. A flaring disk is a disk in which the ratio of disk thickness to the distance to the star, H/r, increases with r; then, any point at the surface of such disks receives direct light from the star, and the disk intercepts a substantial part of the stellar radiation out to large distances. Half of the intercepted light is reradiated away from the disk, and the other half is reradiated down into the disk's deeper layers, providing additional heating to the dust in the optically thick disk interior, which reradiates in the mid-IR, far-IR, and submillimeter wavelengths. The information provided by SED fitting remains limited, because numerous disk parameters are assumed or have not been conclusively determined (*9*). Direct measurements from imaging are therefore required to unambiguously constrain more parameters, such as the overall shape (outer radius and height) of the disk, which determines the amount of starlight captured by the disk. Imaging of disks has been obtained either by observations of the starlight dust scattering (in the visible and near-IR radiation) or of dust thermal emission or by CO lines in the millimeter observations (*3*, *10*, *11*). Scattered starlight observations suffer from the limited contrast offered by imaging devices, and millimeter observations suffer from limited spatial resolution.

A new approach to image disks around HAe stars exploits the fact that about half of them have prominent IR emission bands (IEBs) at 3.3, 6.2, 7.7, 8.6, and 11.3 μm (*12*). These IEBs are believed to arise from the cooling of transiently heated polycyclic aromatic hydrocarbons (PAHs),

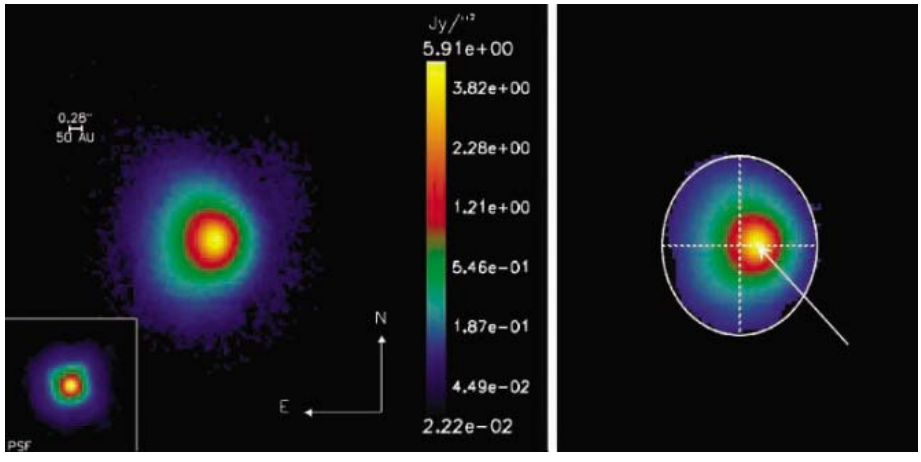

Fig. 1. (**Left**) VISIR false-color image of the emission from the circumstellar material surrounding the HAe star HD 97048 after a deep exposure (36 min). VISIR's PAH1 filter was used; it is centered on the IEB at 8.6 μm and has a full width at half maximum (FWHM) of 0.42 μm. The emission is widely extended, as compared with the point spread function (PSF) (inset) obtained from the observation of the pointlike reference star HD 102964, which was made 15 min before the observation of HD 97048. The measured FWHM of 0.33″ is close to the diffraction limit of 0.28″, also indicated on the figure. The pixel size is 75 milli–arc sec. The noise level is 1.6 millijansky (mJy)/arc sec^2. The photometry, calibrated with HD 102964, yields a total flux of 5.75 (±0.2) Jy. (**Right**) Same image but with a cut at the brightness level of 4.4×10^{-3} Jy/arc sec^2 and a fit of the edge of the image by an ellipse. The dashed lines show the ellipse axis; the ellipse center is offset eastward from the peak flux, as indicated by the arrow.

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which can be excited by the intense stellar ultraviolet radiation (*13*). For a flaring disk, the PAHs at the surface of the disk are in direct view of the central star and can be excited; the resulting IEB emission provides distinguishing information on the disk structure up to large distances from the star. In addition, observing in the mid-IR wavelength alleviates the problem of too much contrast between the photospheric and disk emission. We have thus undertaken a program of imaging "nearby" HAe stars with VISIR (very large telescope imager and spectrometer in the mid-IR) at the European Southern Observatory (ESO) (*14*). One of the first targets was HD 97048, a nearby group I HAe star of spectral type Be9.5/A0 located in the Chameleon I dark cloud, at a distance of 180 parsecs (*15*). The star has a temperature of 10,000 K, a luminosity ($L_\odot$) of 40 solar luminosities, and a mass ($M_\odot$) of 2.5 solar masses (*15*). It is surrounded by a large amount of circumstellar material left from the star formation process, as indicated by the large IR excess (L_{IR}) observed in the SED [L_{IR}~0.40$L_\odot$ (*16*)]. Mid-IR–extended emission has been detected on scales of a few thousand astronomical units and modeled as originating from a dust shell with an inner cavity radius of 180 AU (*17*). Recent long-slit mid-IR spectroscopic observations have revealed a strong resolved emission from the inner region (*18*). Imaging this region with the high-angular resolution offered by a 8-m-size telescope would be a direct way to assess whether HD 97048 is surrounded by a flaring disk, as expected from its rising mid-IR and far-IR SED (*12*).

The observations of HD 97048, conducted on 17 and 19 June 2005, were performed with filters centered on the IEB at 8.6 μm and on the adjacent continuum at 9 μm. The classical mid-IR observing technique of "chopping and nodding" was used, with a chopper throw of 10″ (north-south) and a nodding throw of 8″ (east-west). The 8.6-μm image (Fig. 1) reveals a large extended emission with a strong east-west asymmetry; the brightness isophotal contours are elliptical in shape, and the ellipse centers are offset from the peak of emission. The offset increases when lowering isophotal contours up to a semi-major axis of 2.1″, (Fig. 2 and fig. S1). Such features are characteristic of a flaring disk, vertically optically thick at the wavelength of the observations and inclined to the line of sight (Fig. 3). Beyond 2.1″, the offsets decrease. One possible explanation is that the disk then becomes vertically less optically thick. However, as an alternative explanation, the increasing contribution from the shell emission cannot be disregarded (*17*). We therefore restricted our study to the regions <2.1″, corresponding to an astrocentric distance of 370 AU.

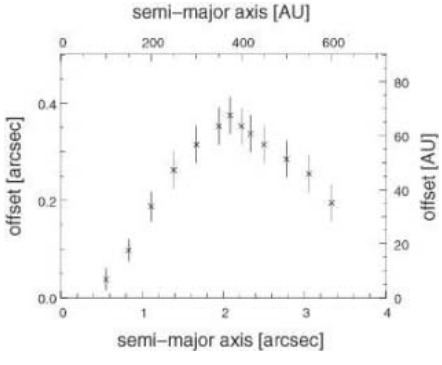

Fig. 2. Offset from the peak flux of the center of the ellipses fitting the image of HD 97048 at various brightness level cuts, as a function of the length of the ellipse semi-major axis (fig. S1). Error bars indicate the uncertainties from ellipse fitting.

To retrieve quantitative information about the disk flaring in these regions, we have fitted the east and west brightness profiles with a simplified model. In this model, the PAH-emitting region is only located at the surface of the disk, whose surface scale height H_s varies with the astrocentric distance following a power law $H_s(r) = H_0.(r/r_0)^\beta$, where H_0 is the disk surface height at the astrocentric distance r_0 and β is the flaring index. We further assumed that the spatial variation of the flux intensity I follows a power law $I(r) = I_0.(r/r_0)^\delta$, where I_0 is the intensity at r_0 and δ is the power law index. This hypothesis is only valid once the continuum emission contribution in the filter at 8.6 μm has been removed, which we have done by extrapolating the continuum emission observed at 9 μm (fig. S2). The result of the fit is shown in Fig. 4; δ for the intensity is found to be –2.3 (+0.2/–0.06), close to the expectation of an index value of –2 for PAH emission (fig. S2), and the disk inclination is 42.8 (+0.8/–2.5) degrees from pole-on. The scale height H_0 is 51.3 (+0.7/–3.3) AU at r_0 = 135 AU and β is 1.26 (±0.05), in agreement with the value expected from hydrostatic, radiative equilibrium models of passive flared disks (*9*). In these models, the flaring structure is supported by the gas, whose vertical scale height H_g is governed by the balance between gas pressure and gravitational pull; the dust plays the key role to capture the starlight and then heat the gas collisionally. H_s corresponds to the upper layers of the disk, where the starlight is intercepted by dust, and is about four times as large as the gas height (*9*). Given the disk's outer radius and scale height, the calculated amount of starlight captured by the disk is 43%, in good agreement with the observed IR excess (*16*).

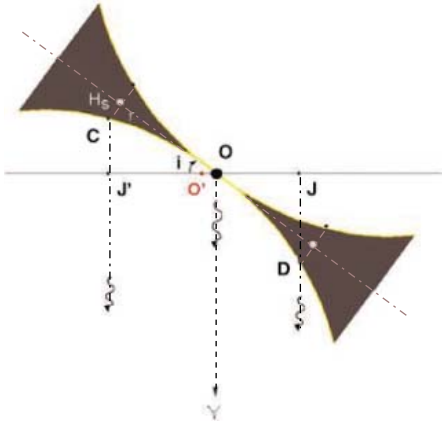

Fig. 3. Sketch of a slice of a flaring disk. The observer is viewing the disk from below (eye symbol). The disk is inclined, from pole-on, by an angle *i*. The disk is optically thick to the ultraviolet and visible starlight along its midplane so that the PAH emission only arises from the disk "surfaces," indicated in yellow. When the disk is also optically thick vertically at the wavelengths of the observations (here in the mid-IR), only the front disk surface is seen by the observer. Consider two points C and D of the front disk surface, located at equal distances from the star (black circle at O). Because of projection effects, the observer views the center of emission from C and D at O′ (red circle), between J and J′, which is offset from O. For a flaring disk, the disk height H_s increases with the distance r to the star, so that the apparent offset increases, as observed for HD 97048. When the disk is vertically optically thin, the front and bottom disk surfaces are both observable, and the disk appears symmetrical with respect to the star. Curved arrows indicate that electromagnetic radiation is emitted toward the observer; gray circles indicate the projection of point C or D onto the disk midplane.

Our observations also provide information about the disk mass. From the observed west-east asymmetry, we can infer that the vertical optical thickness τ at 370 AU is at least 1, implying that, at 370 AU, the dust mass surface density Σ_o is at least $^1/_{1600}$ g cm^{-2} (*19*). Assuming that the astrocentric variation of mass

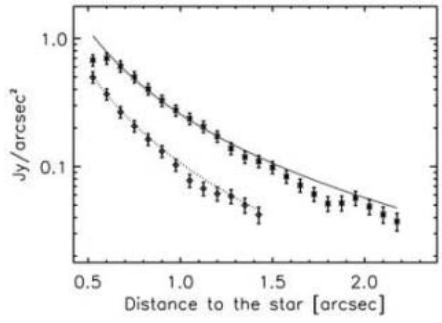

Fig. 4. Fit of the observed east (upper data and solid curve) and west (lower data and dotted line) intensity profiles with a simple flaring disk model. The reduced χ^2 value of the fit is 0.3, well below 1. The error bars indicate the uncertainties in the data due to the background noise and photometric uncertainties from the continuum subtraction (±5% for each image). The range in model parameters has been calculated by exploring the parameter space, which leads to a reduced $\chi^2 < 1$. Below 0.5″, there is no data point, because it is impossible to disentangle reliably the IEB emission from the much larger continuum thermal emission. The angular distance to the star refers to the projected distance on the plane of the sky.

surface density Σ follows a power law $\Sigma(r) = \Sigma_o (r_{AU}/370)^q$, with an index q equal to $-3/2$, as the one inferred for the solar nebula or for extrasolar nebulae (*20*, *21*), we derived a disk dust mass of 40 Earth masses within 370 AU. This lower limit is compatible with the mass of 500 Earth masses derived from the observed 1.3-mm flux (*22*). The dust mass derived here is three to four orders of magnitude larger than the dust mass observed in debris disks and Kuiper belt–like structures found around more-evolved A stars such as β-Pictoris, Vega, Fomalhaut, and HR 4796 (*4*). The dust around these Vega-like stars is thought to be produced by collisions of larger bodies, whose total mass in the case of β-Pictoris has been estimated to be on the order of 100 Earth masses (*23*). Therefore, the dust mass observed around HD 97048 is similar to the mass invoked for the (undetected) parent bodies in more-evolved systems. HD 97048's disk is thus most likely a precursor of debris disks observed around more-evolved A stars. This finding is coherent with the HD 97048 age of ~3 million years, estimated from evolutionary tracks. Another argument in favor of the early evolutionary stage of the system is the presence of a large amount of gas required to support the flaring structure revealed by our observations. Part of the gas has been recently detected, thanks to observations of the molecular hydrogen emission at 2.12 μm (*24*). Assuming that the canonical interstellar gas-to-dust mass ratio of 100 holds, we estimate a total minimum disk mass of 0.01 solar masses, like the estimated minimum mass for the proto-planetary disk around the Sun (*20*).

Because the disk surrounding HD 97048 has a mass surface density comparable to that of the minimum proto-planetary nebula around the Sun, it is worth studying the prospects for planet formation in this environment. Planet formation models are divided into two categories: gravitational instabilities (*25*) and core accretion (*26*). It seems improbable that giant planets will form by means of gravitational instabilities, because the Toomre stability criterion coefficient, equal to $H_g/r\ M_\odot/(r^2\Sigma)$, is >> 1 (*27*). Considering the alternative core accretion scenario by which planets coagulate from initially μm-sized dust (*28*, *29*), it also appears improbable that cores of giant planets are present in the outer regions because of the very long local orbital time scales. Although regions within 40 AU have not been resolved by our observations, it is tempting to extrapolate the surface density from the outer regions and investigate the predictions of planet formation models for the inner regions; inside 10 AU, planetary embryos may be present. Follow-up observations at higher angular resolution with the mid-IR instrument of the ESO Very Large Telescope interferometer will allow probing these regions.

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30. This work was based on observations carried out at the ESO, Paranal, Chile. The VISIR could not have been built without contributions from many people, including G. Durand, Y. Rio, M. Authier, C. Lyraud, and J. Pragt. We also thank A. Palacio, P. Nghiem, and C. Martin for discussions about the age of HD 97048, as well as F. Masset for discussions about gravitational instabilities.

Supporting Online Material

www.sciencemag.org/cgi/content/full/1131436/DC1
Figs. S1 and S2

19 June 2006; accepted 12 September 2006
Published online 28 September 2006;
10.1126/science.1131436
Include this information when citing this paper

The Phase-Dependent Infrared Brightness of the Extrasolar Planet υ Andromedae b

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The star υ Andromedae is orbited by three known planets, the innermost of which has an orbital period of 4.617 days and a mass at least 0.69 that of Jupiter. This planet is close enough to its host star that the radiation it absorbs overwhelms its internal heat losses. Here, we present the 24-micrometer light curve of this system, obtained with the Spitzer Space Telescope. It shows a variation in phase with the orbital motion of the innermost planet, demonstrating that such planets possess distinct hot substellar (day) and cold antistellar (night) faces.

Last year, two independent groups (*1*, *2*) reported the first measurements of the infrared light emitted by extrasolar planets orbiting close to their parent stars. These "hot Jupiter" (*3*) planets have small enough orbits that the energy they absorb from their hosts dominates their own internal energy losses. How they absorb and reradiate this energy is fundamental to understanding the behavior of their atmospheres. One way to address this question is to monitor the emitted flux over the course of an orbit to see whether the heat is distributed asymmetrically about the surface of the planet.

We have observed the υ Andromedae system with the 24-μm channel of the Multiband Imaging Photometer for Spitzer (MIPS) (*4*) aboard the Spitzer Space Telescope (*5*). We took 168 3-s images at each of five epochs spread over 4.46 days (97% of the 4.617-day orbital period of υ Andromedae b) beginning on 18 February 2006 at 12:52 UTC. After rejecting frames with bad pixels near the star and those with Spitzer's "first frame effect" (*1*) (2% to 8% of the data, depending on epoch), we measured the flux of the system and that of the surrounding sky by using both subpixel, interpolated aperture photometry and optimal photometry (*6*, *7*) on each frame.

The detection of eclipses (*8*) from the hot Jupiter planetary systems HD 209458b (*1*), TrES-1 (*2*), and HD 189733b (*9*) demonstrate that a small fraction (~0.1%) of the total infrared light we observe from these systems is actually emitted from the planet rather than the

star. Thus, if we can measure the flux of a system at a signal-to-noise ratio (S/N) > 1000, temperature differences between the day and night faces of the planet will appear as an orbital modulation of the total system flux. With a star as bright as υ Andromedae, our 3-s exposures each have S/N ~ 500, so that our SNR expectation is ~$\sqrt{160} \times 500 \approx 6300$ at each epoch.

The MIPS instrument acquires data by placing the stellar image in a sequence of 14 positions on the detector. The detector's response varies with position at about the 1% level. This variation is stable and reproducible, so we calculated correction factors as follows: At each epoch, we computed the mean measured system flux at each position and took the ratio with the mean in the first position. We then averaged this ratio over all epochs for each position. This results in corrections < 2% between positions, with uncertainties ~ 6×10^{-4}. Bringing the photometry to a common normalization allowed us to average over all the frames in each epoch to achieve S/N ≈ 4350 at each epoch.

As with most infrared instruments, MIPS's sensitivity varies in time. We corrected for such drifts by dividing the system flux value by the measured background in each frame. The background at 24 μm is thermal emission from the zodiacal dust. This dust pervades the inner solar system, absorbing light from the sun and reradiating it at infrared wavelengths. At 24 μm, its emission is strong enough for use as a flux standard, a technique used successfully in measuring the eclipse of HD 209458b (*1*). However, the present work requires one additional correction. The zodiacal background is the integrated emission by dust along the line of sight between the telescope and the object. The observed value thus undergoes an annual modulation as that line of sight varies with the telescope's orbit about the sun. The best available model (*10*) predicts a linear drift over the brief interval of our observations. However, we cannot use the Spitzer model directly, because it is calculated for a line of sight from Earth to the object in question. The difference in position between the Earth-trailing telescope and Earth itself is large enough that the slope of the variation may be slightly different. Thus, we fit for the linear drift directly, simultaneously with any model lightcurve fits.

The phase curve for the υ Andromedae system shows a variation (Fig. 1) in absolute photometry, even before any corrections for instrumental or zodiacal drifts are made. After the calibration with respect to the zodiacal background was applied, this variation is revealed to be in phase with the known orbit of the innermost planet of the system, our principal result.

A simple model can be fit to the phase curve (Fig. 2), assuming local, instantaneous thermal reradiation of the absorbed stellar flux. In the simplest model, the phase of the variation is not a free parameter but is rather set by the measured radial velocity curve (*11*), although phase offsets are possible for models in which the energy is absorbed deep within the atmosphere and redistributed about the surface (*12*, *13*). There is weak (2.5σ) evidence for a small phase offset in this data (Fig. 2), but the large offsets predicted from some models are excluded at high significance. Fitting the peak-to-trough amplitude to the observations yields a best-fit value for the planet-star flux ratio of $2.9 \times 10^{-3} \pm 0.7 \times 10^{-3}$. This is very similar to the result at this wavelength for HD 209458b (*1*). However, the latter is a measure of

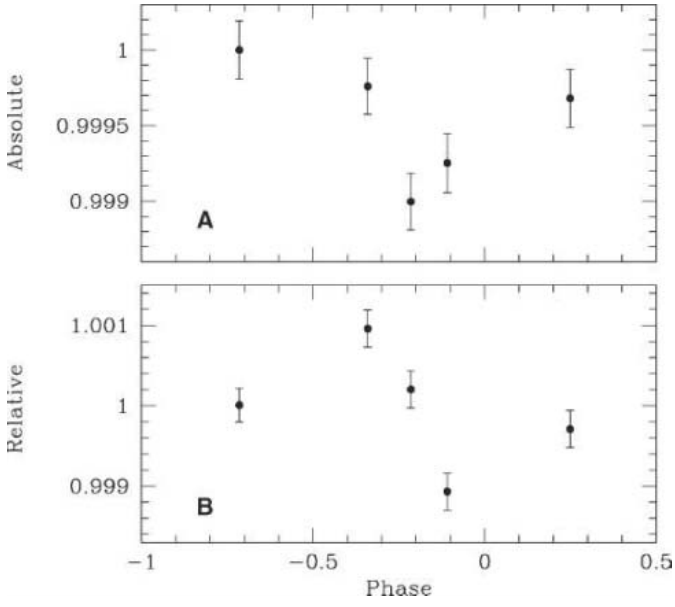

Fig. 1. The light curve of the υ Andromedae system. (**A**) The phase variation in the υ Andromedae system flux before any corrections are applied for instrument or zodiacal drifts. Variations in the system flux are significant even at this point. (**B**) By comparing to the zodiacal background and fitting for the linear drift in the background due to the telescope's motion, we obtained the phase curve shown. In each case, phase is shown modulo unity, with zero phase occurring when the planet is closest to Earth. The amplitude units are expressed in terms of the system flux at the first epoch. Error bars indicate the residual statistical error at each epoch.

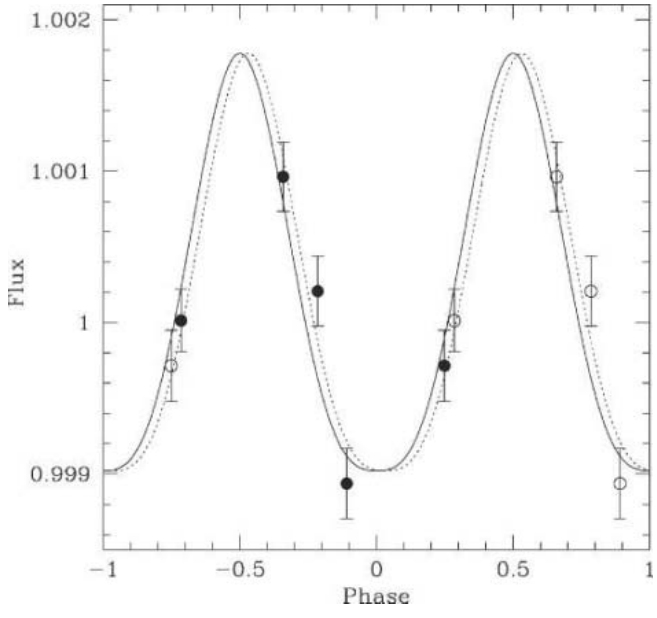

Fig. 2. Comparison of the phase curve and the no-redistribution model. The solid points show our final phase curve, after applying calibrations, in time order from left to right. The open points are repetitions of these, displaced horizontally by one orbit, to better illustrate the phase coverage over two cycles. The solid line is an analytic model for the planetary emission in which energy absorbed from the star is reradiated locally on the day side with no heat transfer across the surface of the planet, the so-called no-redistribution model [and in excellent agreement with the more detailed version in (*17*)]. The assumed inclination in this case is 80° from pole-on, and the relative planet/star amplitude is 2.9×10^{-3}. If we allow for a phase shift relative to the radial velocity curve, we obtain a slightly better fit, as shown by the dotted curve. The best fit is obtained with a phase lag of 11°, but zero lag is excluded only at the 2.5σ level. Error bars indicate the residual statistical error at each epoch.

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the absolute flux from the planet divided by that from the host star, whereas the present result is a measure of the flux difference between the projected day and night sides, divided by the flux of the (different) host star.

Another difference between the cases of υ Andromedae b and HD 209458b is that we do not have a strong constraint on the orbital inclination in this system, so we must include the unknown inclination in the model fit (Fig. 3). At higher inclinations, parts of both the night side and the day side are always visible, so the true contrast between the day and night sides must be larger than the amplitude of the observed variation. This contrast is ultimately driven by the light absorbed from the star, which therefore provides an upper limit. We know the distance of the planet from the star and the stellar properties, so we can estimate the contrast that would result if all of the observed flux were reradiated from the day side and nothing from the night side. If we assume the planet's radius is <1.4 Jupiter radii (as observed for other planets of this class), then we can constrain the expected amplitude to be $<3.4 \times 10^{-3}$ (2σ) for a simple black-body, no-redistribution model with zero albedo. Thus, a consistent picture of the atmospheric energetics emerges as long as the orbital inclination is >30°.

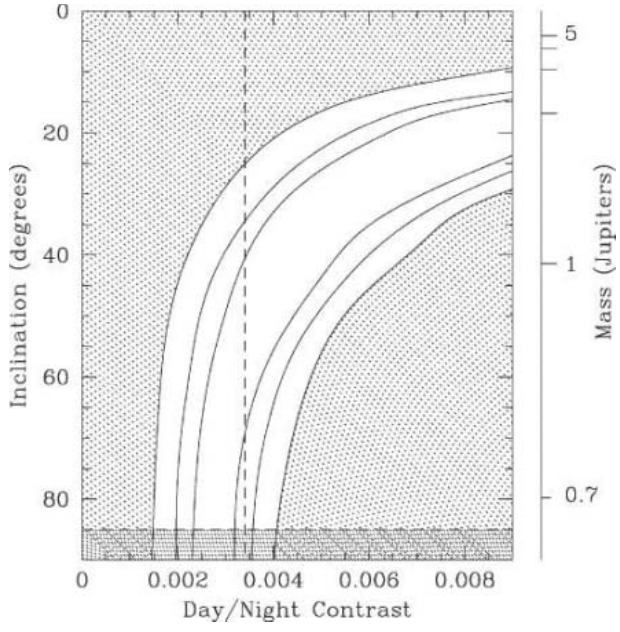

Fig. 3. The influence of inclination on the inferred day-night contrast. The solid contours bound the 1, 2, and 3σ confidence regions for the day-night flux difference (in units of the stellar flux), determined as a function of assumed orbital inclination (measured relative to a face-on orbit). The large shaded regions indicate those values excluded at 3σ. The lower shaded region is excluded because the planet does not transit in front of the star. The vertical dashed line indicates the expected upper limit to the contrast, obtained when the night side is completely dark and all of the stellar flux is reradiated from the day side, in accordance with the no-redistribution model and assuming zero albedo. At the right, we show the true mass of the planet given the assumed inclination (based on the minimum mass derived from the radial velocity curve), in units of Jupiter masses.

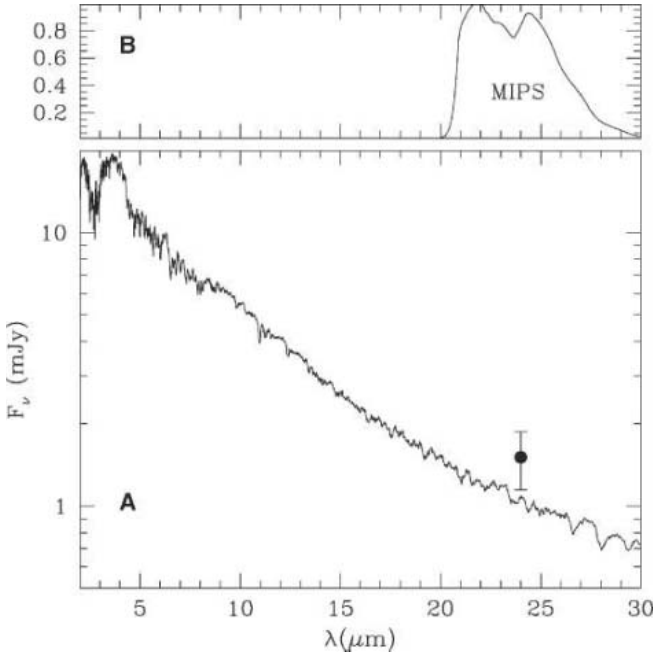

Fig. 4. Comparison of the measured amplitude and a planetary spectral model. (**A**) The solid curve shown is a model (*16*) for a planet of radius $1.4R_J$, irradiated with parameters appropriate to the υ Andromedae system observed at full phase. This results in a temperature ~ 1875 K (*22*). The model is in agreement with the observations (solid circle) at the 2σ level (error bar is 1σ). (**B**) The normalized spectral response curve of the MIPS 24-μm instrument extends from 20 μm to 30 μm.

A natural question to ask is whether there are any plausible alternative models for the observed variation. The estimated rotation period of the star is too long to explain our phase curve as the result of a normal starspot (which is darker than other parts of the stellar surface). One could posit a feature on the stellar surface similar to a starspot but induced by a magnetic interaction between the star and the planet, and therefore moving synchronously with the planet. However, Henry *et al.* (*14*) place an upper limit of 1.6×10^{-4} on the amplitude of optical variation with the planetary orbital period, so infrared variability from the star should be even weaker than this. Some evidence for such magnetospheric interactions is found in observations of chromospheric calcium H and K lines (*15*) and has even been seen in the υ Andromedae system. However, the energy input needed to explain the Ca lines is ~10^{27} ergs s^{-1}, much less than the minimum planetary luminosity we infer here (~4×10^{29} ergs s^{-1}). Indeed, one can make a quite general argument that our observations cannot be powered by the same mechanism, because any heating of the star due to magnetic interaction with the planet ultimately extracts energy from the planetary orbit. Thus, one may calculate an orbital decay time

$$\tau = \frac{GM_* M_p}{2a\dot{E}} = 5 \times 10^6 \text{ year} \left(\frac{M_p}{M_J}\right) \left(\frac{a}{12R_\odot}\right)^{-1} \times \left(\frac{\dot{E}}{10^{30} \text{ergs s}^{-1}}\right)^{-1}$$

where M_* and M_p are the stellar and planetary masses, M_J is the mass of Jupiter, a is the semi-major axis, $R_\odot$ is the radius of the Sun, and $\dot{E}$ is the observed heating rate. Heating at the level necessary to explain our observations would result in the decay of the planetary orbit on time scales < 10^7 years, yet the estimated age of the system is 3 Giga year. As such, the chromospheric heating of the star is unlikely to be related to the effect seen at 24 μm.

This observation reveals the presence of a temperature asymmetry on the surface of an extrasolar planet. The first measurements of eclipses (*1*, *2*) yielded measurements of the absolute flux levels emerging from the day sides of two extrasolar planets. When compared with models of radiative transfer in such atmospheres (*16*–*20*), those observations are consistent with a situation intermediate between no redistribution and full redistribution. A similar comparison is possible in this case (Fig. 4). Our observed day-night flux difference is comparable to the flux emerging at full phase in the models of (*16*), which suggests that there is little redistribution of energy to the night side.

In conclusion, the observation of the phase curve of υ Andromedae b indicates that substantial

temperature differences exist between the day and night faces of the planet, consistent with a model in which very little horizontal energy transport occurs in the planetary atmosphere. Furthermore, it indicates that the opportunities for direct extrasolar planetary observations are better than previously thought, because useful data can be obtained even in cases where the planetary orbit is not so fortuitously aligned that the system exhibits transits or eclipses.

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22. The usual estimate given for planetary temperatures is the equilibrium temperature, T_{eq}, defined as the effective temperature of a uniformly bright planet radiating energy at a rate that balances the irradiation received from the star. T_{eq} is thus determined by the stellar effective temperature, T_{eff}, stellar radius, R_*, and distance of the planet from the star a:

$$T_{eq} = 1744\ \mathrm{K}(T_{eff}/6212\ \mathrm{K})(R_*/1.57R_\odot)^{1/2} \times (a/0.059\mathrm{AU})^{-1/2}$$

in the case of υ and b with albedo = 0.05. However, in a proper no-redistribution model, the temperature distribution is not uniform but rather hottest at the substellar point and coolest at the limb, and the full-phase temperature average over the planetary surface is better approximated by $(2/3)^{1/4}T_{eq}$. This is the temperature we adopt, which is 1875 K in this case.

23. This work is based on observations made with the Spitzer Space Telescope, which is operated by the Jet Propulsion Laboratory, California Institute of Technology, under contract with NASA. Support for this work was provided directly by NASA, its Origins of Solar Systems and Astrophysical Theory programs, as well as the Astrobiology Institute and Spitzer Science Center. We thank the personnel of the Spitzer Science Center and its MIPS instrument, who ultimately made these measurements possible.

15 August 2006; accepted 18 September 2006
Published online 12 October 2006;
10.1126/science.1133904
Include this information when citing this paper.

Brownian Motion of an Ellipsoid

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We studied the Brownian motion of isolated ellipsoidal particles in water confined to two dimensions and elucidated the effects of coupling between rotational and translational motion. By using digital video microscopy, we quantified the crossover from short-time anisotropic to long-time isotropic diffusion and directly measured probability distributions functions for displacements. We confirmed and interpreted our measurements by using Langevin theory and numerical simulations. Our theory and observations provide insights into fundamental diffusive processes, which are potentially useful for understanding transport in membranes and for understanding the motions of anisotropic macromolecules.

Brownian motion (*1*), wherein small particles suspended in a fluid undergo continuous random displacements, has fascinated scientists since before it was first investigated by the botanist Robert Brown in the early 19th century. The origin of this mysterious motion was largely unexplained until Einstein's famous 1905 paper (*2*) that established a relation between the diffusion coefficient of a Brownian particle and its friction coefficient. One year later (*3*), Einstein extended the concept of Brownian dynamics to rotational and other degrees of freedom. The subsequent study of Brownian motion and its generalizations has had a profound impact on physics, mathematics, chemistry, and biology (*4*). Because direct detection of translational Brownian motion is relatively easy, many experiments elucidating the ideas of translational diffusion have been carried out. On the other hand, the direct visualization of rotational Brownian motion has not been an easy task, and fundamental concepts about motions of anisotropic macromolecules remain untested. For this contribution, we used digital video microscopy to study the Brownian motion of an isolated ellipsoid in suspension and thus directly observed the coupling effects between rotational and translational motion.

Particle anisotropy leads to dissipative coupling of translational to rotational motion and to physics first explored by F. Perrin (*5*, *6*). A uniaxial anisotropic particle is characterized by two translational hydrodynamic friction coefficients, γ_a and γ_b, respectively, for motion parallel and perpendicular to its long axis. If a particle's rotation is prohibited, it will diffuse independently in directions parallel and perpendicular to its long axis with respective diffusion constants of $D_\alpha = k_BT/\gamma_\alpha$ for α either a or b, where k_B is Boltzmann's constant and T is the temperature. In general, γ_a is less than γ_b (*7*), and consequently D_a is greater than D_b. If rotation is allowed, rotational diffusion, characterized in two dimensions by a single diffusion coefficient, D_θ, and associated diffusion time, $\tau_\theta = 1/(2D_\theta)$, washes out directional memory and leads to a crossover from anisotropic diffusion at short times to isotropic diffusion at times much longer than τ_θ. Figure 1, A and B, presents numerical simulations (*8*) that illustrate this behavior. Our experiments, which were restricted to two dimensions (2D), provide explicit verification of this behavior and some of its extensions. In addition, we show that a fundamental property of systems with dissipatively coupled translation and rotation is the existence of non-Gaussian probability density functions (PDFs) for displacements in the lab frame.

Micrometer-sized PMMA (polymethyl methacrylate) uniaxial ellipsoids (*9*) were under strong quasi–two-dimensional confinement in a thin glass cell. The choice of 2D rather than 3D for these studies substantially simplified the experimental imaging tasks as well as the data acquisition time and storage requirements. The choice also ensured that the measured effects would be large by virtue of the much larger friction anisotropy in 2D compared with 3D. The local cell thickness was ~1 μm. It was measured to within 0.1 μm resolution by comparing the Michel-Levy chart (*10*) to the reflected interference colors produced by the two inner surfaces under white light illumination on the microscope (Fig. 1D). To avoid interactions between ellipsoids, we made the solution very dilute. The Brownian motion of a single ellipsoid in water was recorded by a charge-coupled device (CCD) camera on a videotape at 30 frame/s. From the image analyses, we obtained data sets consisting of a particle's center-of-mass positions

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$\mathbf{x}(t_n) = [x(t_n), y(t_n)]$ in the lab frame and its orientation angles $\theta(t_n)$ relative to the x axis at times $t_n = n(1/30)$ s, as shown in Fig. 1F. The orientational resolution is 1°, and spatial resolutions are 0.5 pixel = 40 nm along the particle's short axis and only 0.8 pixel along its long axis because of the superimposed small tumbling motion. We define each 1/30-s time interval as a step. During the nth step, the particle's position changes by $\delta\mathbf{x}(t_n) = \mathbf{x}(t_n) - \mathbf{x}(t_{n-1})$ and its angle by $\delta\theta(t_n) = \theta(t_n) - \theta(t_{n-1})$. From the data set, we extract an ensemble of particle trajectories starting at different times τ_0 and ending a time t later. The total positional and angular displacements in these trajectories are, respectively, $\Delta\mathbf{x}(t) = \mathbf{x}(t + \tau_0) - \mathbf{x}(\tau_0)$ and $\Delta\theta(t) = \theta(t + \tau_0) - \theta(\tau_0)$.

We first consider the statistical properties of $\theta(t)$, which, as pointed out by Perrin (*6*), are independent of translational motions. We measured data from a 30-min trajectory of a 2.4 μm–by–0.3 μm–by–0.3 μm ellipsoid confined in an 846-nm-thick cell (Fig. 2A). The inset shows that the mean-square angular displacement $\langle[\Delta\theta(t)]^2\rangle$ equals $2D_\theta t$, where the average $\langle\ \rangle$ is over all trajectories with different starting times τ_0. The mean-square angular displacement has diffusive behavior over the entire range of observable times with a rotational time of $\tau_\theta = 1/(2D_\theta) = 3.1$ s. Over the time scales we can observe, this diffusive behavior is independent of θ_0. The PDF for $\Delta\theta(t)$ was measured to be Gaussian with variance $2D_\theta t$, and the angles $\theta(t)$ were measured to be uniformly distributed in $[0,2\pi]$.

We now turn to the statistics of translational motion whose full understanding is facilitated by the consideration of decomposing the displacement $\delta\mathbf{x}_n$ into its components $\delta\tilde{x}_{ni}$ relative to the body frame or δx_{ni} relative to the fixed lab frame. As shown in Fig. 1C, the two are related via a rotation, $\delta\tilde{x}_{ni} = R_{ij}\delta x_{nj}$, where the Einstein summation convention on repeated indices is understood and $R_{ij} = \begin{pmatrix} \cos\theta_n & \sin\theta_n \\ -\sin\theta_n & \cos\theta_n \end{pmatrix}$ is the rotation matrix with $\theta_n = [\theta(t_{n-1}) + \theta(t_n)]/2$. In practice, choosing $\theta_n = \theta(t_{n-1})$ or $\theta_n = \theta(t_n)$ has little effect on our results because θ barely changes during 1/30 s. We can construct total body-frame displacements by summing over displacements in each step, $\tilde{x}(t_n) = \sum_{k=1}^{n}\delta\tilde{x}_k$, and from $\tilde{x}(t_n)$ we can construct body-frame displacements for trajectories of duration t at starting time τ_0 via $\Delta\tilde{x}(t) = \tilde{x}(t + \tau_0) - \tilde{x}(\tau_0)$.

Mean-square displacements (MSDs) in the body frame and in the lab frame were averaged over all trajectories with different initial angle $\theta_0 \equiv \theta(\tau_0)$ (Fig. 2A). They are all diffusive with $\langle[\Delta\tilde{x}(t)]^2\rangle = 2D_a t$, $\langle[\Delta\tilde{y}(t)]^2\rangle = 2D_b t$, and $\langle[\Delta x(t)]^2\rangle = \langle[\Delta y(t)]^2\rangle = (D_a + D_b)t \equiv 2\overline{D}t$. The full average $\langle\ \rangle$ for any observable A can be viewed as an ensemble average of trajectories at fixed θ_0 followed by a second average over all θ_0: $\langle A\rangle = [\langle A\rangle_{\theta_0}]_{\mathrm{av}} = \frac{1}{2\pi}\int_0^{2\pi} d\theta_0\langle A\rangle_{\theta_0}$.

A particle with a given initial angle will diffuse more rapidly along its long axis than along its short axis. As time progresses, however, memory of its initial direction is lost, and diffusion becomes isotropic. Thus, averages over trajectories at fixed θ_0 should exhibit a crossover from early-time anisotropic to late-time isotropic diffusion. Our measurements with $\theta_0 = 0$ of the time-dependent diffusion coefficients $D_{xx}(t) = \langle[\Delta x(t)]^2\rangle_0/(2t)$ and $D_{yy}(t) = \langle[\Delta y(t)]^2\rangle_0/(2t) = \langle[\Delta x(t)]^2\rangle_{\frac{\pi}{2}}/(2t)$ provide direct verification of this crossover (Fig. 2B): At $t << \tau_\theta$, D_{xx} equals D_a and D_{yy} equals D_b, whereas for $t >> \tau_\theta$, D_{xx} equals D_{yy} equals $\overline{D}$.

The anisotropic-to-isotropic crossover was calculated in 3D by Perrin (*6*) and is mentioned in qualitative terms in a 3D simulation (*11*). We calculate the properties of this transition in 2D within the Langevin formalism and compare them with experiment. Because our time scales are much larger than the momentum relaxation times of a micrometer-sized particle in water ($I/\gamma_{\mathrm{rot}} \sim m/\gamma \sim 10^{-7}$ s), we can ignore inertial terms. The Langevin equations for displacement and angle in the lab frame in the presence of external forces described by a Hamiltonian H are

$$\partial_t x_i = -\Gamma_{ij}(\theta)\frac{\partial H}{\partial x_j} + \xi_i(t) \qquad (1a)$$

$$\partial_t \theta = -\Gamma_\theta\frac{\partial H}{\partial \theta} + \xi_\theta \qquad (1b)$$

where $i = x,y$ for 2D and $\Gamma_{ij} = \gamma_{ij}^{-1}$ is the mobility tensor, which can be expressed in terms of the unit vector $\mathbf{n}(t) \equiv \mathbf{n}[\theta(t)]$ specifying the direction of the local anisotropy axis as $\Gamma_{ij}(t) = \Gamma_b\delta_{ij} + \Delta\Gamma n_i(t)n_j(t) = \Gamma\delta_{ij} + \Delta\Gamma M_{ij}[\theta(t)]/2$, where $\Gamma = (\Gamma_a + \Gamma_b)/2$, $\Delta\Gamma = \Gamma_a - \Gamma_b$, and $M_{ij}(\theta) = \begin{pmatrix} \cos 2\theta & \sin 2\theta \\ \sin 2\theta & -\cos 2\theta \end{pmatrix}$. $\xi_\theta(t)$ and $\xi_i(t)$ are ran-

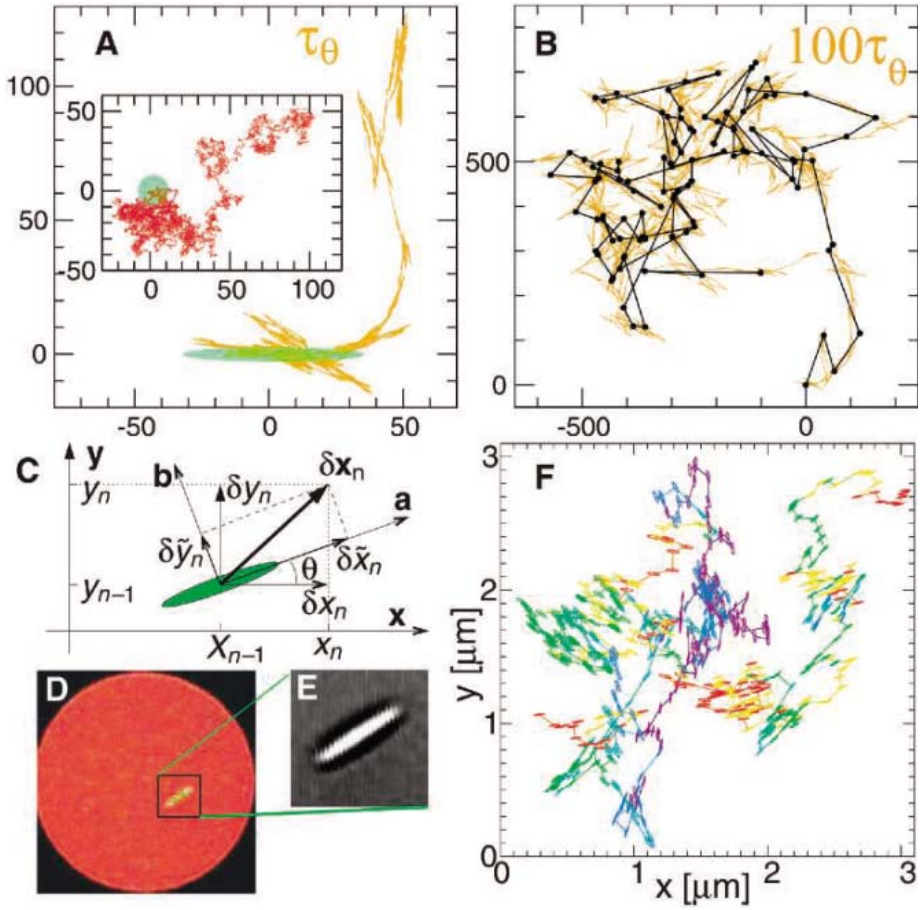

Fig. 1. (**A** and **B**) 10,000-step 2D random walk trajectories for an ellipsoid with $D_a = 0.99$ and $D_b = 0.01$ during τ_θ and $100\tau_\theta$, respectively. τ_θ is the time for the ellipsoid to diffuse 1 rad. (A Inset) 10,000-step trajectory for a sphere with $D_a = D_b = 0.5$ during τ_θ. The initial positions are represented by a green ellipse and a sphere. At step times long compared with τ_θ, the coarse-grained 100-step black trajectory in (B) is similar to that of the random walk of a spherical particle in fig. S1. (**C**) Representation of an ellipsoid in the x-y lab frame and the $\tilde{x}$-$\tilde{y}$ body frame. The angle between two frames is $\theta(t)$. The displacement $\delta\mathbf{x}$ can be decomposed as $(\delta x, \delta y)$ or $(\delta\tilde{x}, \delta\tilde{y})$. (**D**) True interference color in the reflection mode of the microscope. (**E**) Ellipsoid image in the transmission mode. (**F**) A typical 20-s experimental trajectory with step 1/30 s. $D_a/D_b = 4.07$. Orientations are further labeled with a rainbow color scale. For example, the purple parts of the trajectory reflect a higher mobility along the y direction, and the red parts reflect a higher mobility along the x direction.

dom noise sources with zero mean and respective variances, $\langle \xi_\theta(t)\xi_\theta(t')\rangle = 2k_BT\Gamma_\theta\delta(t-t') = 2D_\theta\delta(t-t')$ and $\langle \xi_i(t)\xi_j(t')\rangle_{\theta(t)} = 2k_BT\Gamma_{ij}[\theta(t)]\delta(t-t')$, dictated by the Einstein relation or equivalently by the requirement that thermal equilibrium be reached at long times. We retain H in Eq. 1 even though the external forces are zero in our experiments to emphasize that the mobilities Γ_{ij} and Γ_θ relating velocity and angular velocity to force and torque, respectively, determine the variances of the random noise sources. $\xi_\theta(t)$ obeys Gaussian statistics at all times, as does $\xi_i(t)$ for a fixed angle $\theta(t)$. The average $\langle A\rangle_{\theta_0}$ of any measurable quantity is equivalent to the average of A over both $\xi_i(t)$ and $\xi_\theta(t)$ at fixed θ_0.

Because there are no external forces in our experiments, we can set $\partial H/\partial x = 0$ and $\partial H/\partial\theta = 0$. Equation 1b for $\theta(t)$ is simply the Langevin equation for 1D diffusion. It yields a time-independent diffusion coefficient $D_\theta = \langle[\Delta\theta(t)]^2\rangle/(2t)$, a Gaussian PDF for $\Delta\theta(t)$ with variance $2D_\theta t$, and consequently $\langle\cos n\Delta\theta(t)\rangle = \mathrm{Re}\langle e^{in\Delta\theta(t)}\rangle = \cos n\theta_0 e^{-n^2D_\theta t}$. From this we can calculate (*8*) the time-dependent displacement diffusion tensor for fixed θ_0:

$$D_{ij}(t,\theta_0) = \langle[\Delta x_i(t)][\Delta x_j(t)]\rangle_{\theta_0}/(2t) = \bar{D}\delta_{ij} + \frac{\Delta D}{2}\frac{\tau_4(t)}{t}M_{ij}(\theta_0) \qquad (2)$$

where $\Delta D \equiv D_a - D_b$ and $\tau_n(t) \equiv \int_0^t dt' e^{-nD_\theta t'} = (1 - e^{-nD_\theta t})/(nD_\theta)$. $D_{xx}(t,0)$ and $D_{yy}(t,0)$ quantitatively match experimental results for $\theta_0 = 0$ as shown in Fig. 2B, with D_a, D_b, and D_θ equal to their values obtained from Fig. 2A. The average of $D_{ij}(t, \theta_0)$ in Eq. 2 over initial angles θ_0 yields $\bar{D}_{xx} = \bar{D}_{yy} = \bar{D}$, in agreement with the MSDs of x and y in Fig. 2A. The 3D counterpart, $\bar{D}_{xx} = \bar{D}_{yy} = \bar{D}_{zz} = (D_a + D_b + D_c)/3$, is widely used in dynamic light scattering (*12*).

Unlike spheres, anisotropic particles have anisotropic friction coefficients that are responsible for the coupling of translation and rotation. This coupling leads to nontrivial mixed correlation functions such as

$$\langle\Delta x_i\Delta x_j e^{in\theta}\rangle/t = [2\bar{D} + \Delta D A_{ij}^{(n)}(t)/2]e^{in\theta_0 - n^2D_\theta t} \qquad (3)$$

where $A^{(n)}_{ij}(t) = e^{j2\theta}\tau_{(4+4n)}\begin{pmatrix}1 & -i\\ -i & -1\end{pmatrix} + e^{-i2\theta}\tau_{(4-4n)}\begin{pmatrix}1 & i\\ i & -1\end{pmatrix}$. Equation 3 is obtained from our Langevin formalism (*8*). Experimental results agree well with these theoretical predictions and deviate from the theoretical dashed curves obtained assuming translational and rotational motion are decoupled (Fig. 2C).

Transforming Eq. 1a into the body frame at $\partial H/\partial x = 0$, we obtain

$$\partial_t\tilde{x}_i = \tilde{\xi}_i(t) = R_{ij}[\theta(t)]\xi_j(t) \qquad (4)$$

The probability distribution of $\tilde{\xi}i(t)$, which can be calculated directly from its definition and the properties of $\xi_i(t)$, is a Gaussian with zero mean and variance $\langle\tilde{\xi}_i\tilde{\xi}_j\rangle = 2k_BT\tilde{\Gamma}_{ij}\delta(t-t')$, where $\tilde{\Gamma}_{ij}$ is a $\theta(t)$-independent diagonal matrix with components $\tilde{\Gamma}_{xx} = \Gamma_a$ and $\tilde{\Gamma}_{yy} = \Gamma_b$. Thus, $\langle(\Delta\tilde{x}_i)^2\rangle$ equals $2D_it$, where $D_i = (D_a, D_b)$, in agreement with the experimental data in Fig. 2A. Because $\tilde{\xi}_i$ is Gaussian, the PDF for body-frame displacements $\Delta\tilde{x}_i$ (*t*) is Gaussian at all times:

$$f_{\Delta\tilde{x}_i}(x,t) = \frac{1}{\sqrt{2\pi}\sigma_i(t)}e^{-\frac{x^2}{2\sigma_i^2(t)}} \qquad (5)$$

where $\sigma_i^2(t) = 2D_it$. Our measurements confirm this behavior in fig. S1. For our quasi-2D sample, the ellipsoid's friction and diffusion tensors are different at different heights within the cell (*13*). Therefore, the PDF of $\Delta\tilde{x}_i$ should be an average of Gaussian PDFs with different variances. However, the interference color from the ellipsoid changed very little throughout the course of our experiment; from this result we estimate that the ellipsoid remains within 50 nm of the midplane of the cell and that the non-Gaussian effects are too small to be observable as is confirmed by our measurements.

Although the statistics of displacements in the body frame are Gaussian, those in the lab frame are not because of coupling between translation and rotation (*14*). Prager (*15*) calculated the non-Gaussian concentration for averaged initial angles in a particular geometry in three dimensions. The lab-frame noise, $\xi_i(t) = R_{ij}^{-1}[\theta(t)]\ \tilde{\xi}_i(t)$, is a nonlinear function of the independent noises $\xi_\theta(t)$ and $\tilde{\xi}_i(t)$. Thus, although its probability distribution is Gaussian for fixed $\theta(t)$ and thus fixed $\xi_\theta(t)$, its distribution averaged over $\xi_\theta(t)$ is non-Gaussian, as is that for $\Delta x_i(t)$. At short times, the lab- and body-frame displacements are equal, and the PDF for $\Delta x_i(t)$ is Gaussian because that for $\Delta\tilde{x}_i(t)$ is. Directional information is lost at times greater than τ_θ. Therefore, at long times, $\Delta\mathbf{x}(t)$ is a sum of displacements from $\sim t/\tau_\theta$ statistically independent steps, and the central limit theorem implies that its PDF is Gaussian. Thus at fixed θ_0, we expect deviation from Gaussian behavior to vanish at $t = 0$ and $t = \infty$ and to reach a maximum at times of order τ_θ.

The simplest manifestations of non-Gaussian behavior are the nonzero values of the fourth- or higher-order cumulants of lab-frame displacements, which can be calculated (*8*) from our Langevin theory. For example, the fourth cumulant of $\Delta x(t)$ for fixed initial orientation is

$$C^{(4)}_{\theta_0}(t) = \langle[\Delta x(t)]^4\rangle_{\theta_0} - 3\langle[\Delta x(t)]^2\rangle^2_{\theta_0} = \frac{1}{2}(\Delta D)^2\left\{3[\tau_\theta t - \tau_\theta\tau_4(t) - \tau_4(t)^2] + [\tau_\theta\tau_4(t) - \tau_\theta\tau_{16}(t) - 3\tau_4(t)^2]\cos 4\theta_0\right\} \qquad (6)$$

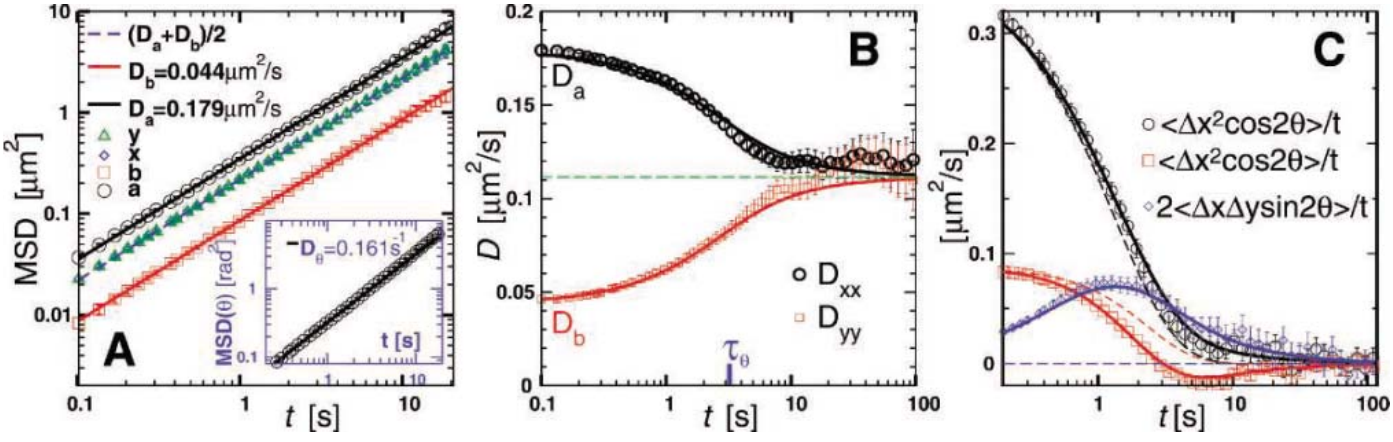

Fig. 2. (**A**) MSDs along *a*, *b*, *x*, and *y* axes. (Inset) Angular MSD. All curves have diffusive behavior ($\propto t$), and corresponding diffusion coefficients D = MSD/(2*t*) shown in the figure are from best fits. (**B**) Diffusion coefficients D in the lab frame. The initial orientation of each trajectory was chosen to be along the x axis ($\theta_0 = 0$), so that D_{xx} and D_{yy} change from D_a and D_b to $\bar{D}$, respectively, over time interval τ_θ. Symbols, experiment; error bars $\propto\sqrt{t}$. Solid curves, Eq. 2 when $\theta_0 = 0$. (**C**) Mixed correlations of translational displacements and orientation. Symbols, experiment. Error bars $\propto\sqrt{t}$. Solid curves, theoretical results from Eq. 3 for $n = 2$. Dashed curves, reference uncorrelated averages $\langle\Delta x^2\rangle\langle\cos 2\theta\rangle/t$, $\langle\Delta y^2\rangle\langle\cos 2\theta\rangle/t$, and $2\langle\Delta x\Delta y\rangle\langle\sin 2\theta\rangle/t = 0$.

This function vanishes as t^{2+s_2}, where $s_2 > 0$, as $t \to 0$ and grows linearly in t as $t \to \infty$. The non-Gaussian parameter,

$$p(t,\theta_0) = \frac{C^{(4)}_{\theta_0}(t)}{3\langle[\Delta x(t)]^2\rangle^2_{\theta_0}} = \frac{C^{(4)}_{\theta_0}(t)}{3[2\,\bar{D}t + \Delta D\tau_4(t)\cos 2\theta_0]^2} \quad (7)$$

vanishes with t^{s_2} for $t \to 0$ and as t^{-1} as $t \to \infty$. The angle-averaged non-Gaussian parameter,

$$\bar{p}(t) = \frac{\bar{C}^{(4)}(t)}{3\langle[\Delta x(t)]^2\rangle^2} = \frac{\Delta D^2}{8\bar{D}^2}\frac{\tau_\theta[t - t_4(t)]}{t^2} \quad (8)$$

$$\xrightarrow{t\to 0} \quad \frac{(D_a/D_b - 1)^2}{2(D_a/D_b + 1)^2} \quad (9)$$

where $\bar{C}^{(4)}(t) = \langle[\Delta x(t)]^4\rangle - 3\langle[\Delta x(t)]^2\rangle^2$, approaches a constant as $t \to 0$ and vanishes as t^{-1} as $t \to \infty$. Because statistics in the body frame are Gaussian, the body-frame non-Gaussian parameter $p_b(t)$ is zero.

Equations 7 and 8 are confirmed numerically in Fig. 3A. Experimental measurements of both $p(t,\theta_0)$ and $\bar{p}(t)$ have poor statistics at large t because their errors grow as $t^{3/2}$. Nevertheless, we were able to extrapolate to the $t \to 0$ limit of $\bar{p}(t)$ in seven samples with different aspect ratios and to confirm Eq. 9 in the Fig. 3A inset. Figure 3A confirms our qualitative expectations about the non-Gaussian parameter p in different frames and for different types of averages, specifically: (i) In the ensemble with fixed θ_0, the non-Gaussian parameter vanishes for $t \ll \tau_\theta$ and $t \gg \tau_\theta$ and reaches a maximum when $t \sim \tau_\theta$; (ii) in the ensemble that averages over θ_0, the non-Gaussian parameter is a maximum at $t = 0$ and vanishes for $t \gg \tau_\theta$; and (iii) larger D_a/D_b causes larger non-Gaussian effects.

It is clear from Eqs. 6 to 9 that non-Gaussian behavior originates in particle anisotropy and vanishes when ΔD vanishes. Thus, non-Gaussian effects for anisotropic particles diffusing in 3D with stick boundary conditions should be small because $1 < D_a/D_b = \gamma_b/\gamma_a < 2$ when $1 < a/b < \infty$ (*5*, *7*). For some small molecules, the slip boundary condition is more appropriate (*16*, *17*) and γ_b/γ_a diverges (*11*) even in 3D. Under quasi-2D conditions with stick boundary conditions, however, D_a/D_b increases with aspect ratio and finally saturates (*13*) at a value much larger than 2. In summary, non-Gaussian effects are strong when $D_a \gg D_b$, i.e., for particles with a high aspect ratio confined in quasi-2D (in our case, D_a/D_b reaches about 4) or for some molecules with slip boundary conditions.

Lastly, we consider the lab-frame PDF for $\Delta x(t)$. The expectation is that these PDFs at fixed θ_0 will be non-Gaussian and exhibit maximum deviations from Gaussian behavior at times of order τ_θ. We have verified that this is the case within our statistical errors, but the deviations are very small. The lab-frame PDF averaged over θ_0 shows more striking deviations from Gaussian behavior (*8*), particularly as $t \to 0$:

$$f_{\Delta x}(x) = \langle\delta[x - \Delta x(t)]\rangle \xrightarrow{t\to 0} \int_0^{2\pi}\frac{d\theta}{2\pi}\frac{e^{-\frac{x^2}{2\sigma^2(\theta)}}}{\sqrt{2\pi}\sigma(\theta)} \quad (10)$$

where $\sigma^2(\theta) = \sigma_a^2\cos^2\theta + \sigma_b^2\sin^2\theta$ with $\sigma_i^2 = 2D_i t$. The physical meaning of Eq. 10 is apparent. When $t \to 0$, the orientation θ does not change during the displacement. Those Δx with the same θ_0 follow a Gaussian distribution with $\sigma = \sigma(\theta_0)$ because the hydrodynamic drag coefficient $\gamma(\theta_0)$ is a constant. Averaging Gaussian PDFs with different θ_0 over $[0,2\pi]$ yields a non-Gaussian PDF as shown in Eq. 10.

Experimental angle-averaged PDFs of lab-frame displacement are shown (Fig. 3B) at time intervals of $t = 0.1$ s. The system's isotropy is confirmed by $f_{\Delta x}(x) = f_{\Delta y}(x)$. Interestingly, there are more tiny and large steps and fewer middle-sized steps than there are in a Gaussian distribution (fig. S2). This PDF agrees with Eq. 10 very well with no free parameters. We measured the PDFs of 15 samples with different aspect ratios at different confinements. All agreed with Eq. 10. When $D_a/D_b < 2.5$, the measured non-Gaussian PDF becomes indistinguishable from a Gaussian distribution.

The most common experimental probes typically measure only second moments, from which diffusion coefficients can be extracted, that provide no information about non-Gaussian behavior. For example, dynamic light scattering (*12*, *18*) and nuclear magnetic resonance (NMR) (*19*) measure θ_0-averaged translational diffusion coefficients of anisotropic constituents; and NMR (*19*), fluorescence depolarization (*20*), electric birefringence (*21*), dichroism (*22*), and depolarized dynamic light scattering (*19*) measure rotational diffusion coefficients. In principle, some of these probes, light scattering in particular, could provide a measure of $\bar{C}^{(4)}(t) \xrightarrow{t\to 0} 3(\Delta D)^2 t^2/2$ and higher moments, but we are not aware of any such measurements. Certainly, the non-Gaussian effects would be very small, especially for particles in 3D where $D_a/D_b < 2$.

Our observations using digital video microscopy of the Brownian motion of an isolated ellipsoid in two-dimensions provide exquisitely detailed information about the diffusive properties of anisotropic objects and the subtle interplay between orientational and translational motions. Besides providing us with new insights about a fundamental phenomenon, these observations and underlying theory are potentially useful for research on diffusion of anisotropic molecules in membranes (*16*), on the hydrodynamics and kinetics of ensembles of anisotropic particles, and on anisotropic molecules that

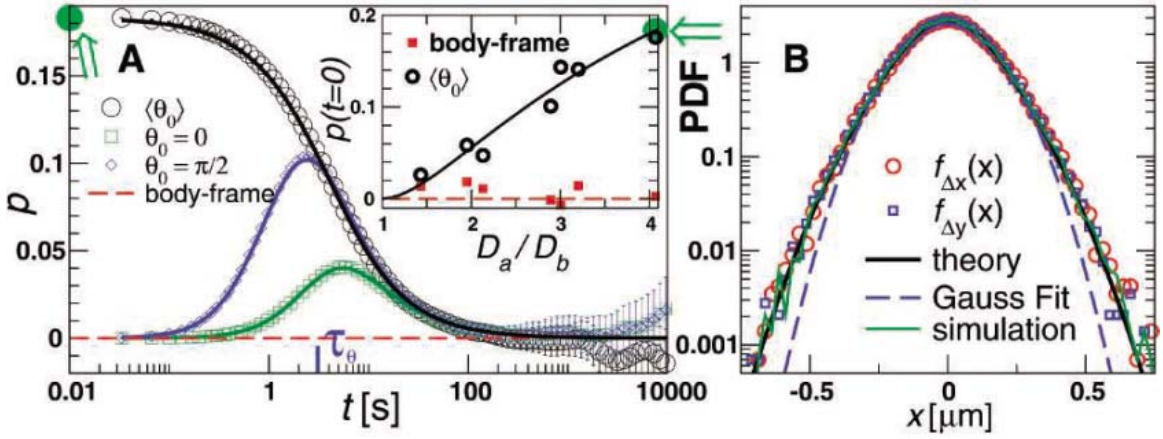

Fig. 3. (**A**) Non-Gaussian parameters as a function of t. Symbols, simulation in the lab frame for an ellipsoid with D_a, D_b, and D_θ from Fig. 2A. Error bars $\propto t^{3/2}$. Curves, theoretical predictions for $p(t,0)$ and $p(t,\pi/2)$ in Eq. 7 and $\bar{p}(t)$ in Eq. 8. Dashed line, $p_b(t) = 0$ in the body frame. (Inset) $\bar{p}(t = 0)$ for ellipsoids with different aspect ratios and confinements. Symbols, experiments; curve, theoretical prediction of Eq. 9. The double arrows in the figure and the inset indicate equivalent points for which PDFs are shown in (B). (**B**) Lab-frame PDFs for $\Delta x(t)$ and $\Delta y(t)$ at $t = 0.1$ s. Measured $f_{\Delta x}(x)$ (open circles) and $f_{\Delta y}(x)$ (open squares) agree with the theory (solid dark curve) of Eq. 10 with no free parameter ($\sigma_a = \sqrt{2D_a}t$, with D_a from the fit of Fig. 2A). Dashed curve, best Gaussian fit; light curve, simulation.

experience slip boundary conditions and thus have a large ratio of γ_a to γ_b.

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23. We are grateful to M. Goulian for a careful reading of this manuscript. This work is supported by the MRSEC grant DMR-0520020 and NSF grant DMR-0505048.

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5799/626/DC1
Materials and Methods
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18 May 2006; accepted 15 September 2006
10.1126/science.1130146

α-Hydroxy and α-Amino Acids Under Possible Hadean, Volcanic Origin-of-Life Conditions

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To test the theory of a chemoautotrophic origin of life in a volcanic, hydrothermal setting, we explored mechanisms for the buildup of bio-organic compounds by carbon fixation on catalytic transition metal precipitates. We report the carbon monoxide–dependent formation of carbon-fixation products, including an ordered series of α-hydroxy and α-amino acids of the general formula R-CHA-COOH (where R is H, CH_3, C_2H_5, or $HOCH_2$ and A is OH or NH_2) by carbon fixation at 80° to 120°C, catalyzed by nickel or nickel,iron precipitates with carbonyl, cyano, and methylthio ligands as carbon sources, with or without sulfido ligands. Calcium or magnesium hydroxide was added as a pH buffer. The results narrow the gap between biochemistry and volcanic geochemistry and open a new gateway for the exploration of a volcanic, hydrothermal origin of life.

The theory of a volcanic, hydrothermal, chemoautotrophic origin of life postulates a locally and temporally coherent, evolvable system of autocatalytic, synthetic carbon-fixation pathways, catalyzed by inorganic transition metal precipitates (*1*–*4*) and generating low molecular weight organic compounds from highly oxidized precursors. Here, this system of pathways is termed "pioneer metabolism." In accordance with the principle of metabolic continuity, the theory assumes a step-by-step evolutionary changeover by evolution of ligand feedback from racemic ligands of the inorganic transition metal precipitates to homochiral metalloenzymes of extant organisms (*3*, *4*). In a continuing effort to establish an experimental grounding for this hypothesis, we experimentally explored the viability of volcanic, hydrothermal carbon-fixation pathways using CO and CN^- as carbon sources.

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We chose Ni or Ni,Fe precipitates as catalytic transition metals because of the catalytic roles of these biometals (as sulfide or hydroxide complexes) in our previous experiments (*5*, *6*); (Ca, Mg)$(OH)_2$ as source for hydroxy ligands and for buffering against acidification; Na_2S or CH_3-SNa as sources for sulfido or methylthio ligands; and CO and KCN as sources for carbonyl and cyano ligands in accordance with extant [Fe,Ni]- and [Fe,Fe]-hydrogenases (*7*).

The reaction conditions are listed in Table 1. Unless stated otherwise, the experiments were carried out in a slurry with 10 ml of H_2O and ^{13}C-labeled KCN (*8*). The alkaline pH range is in agreement with the pH requirement of peptide synthesis (*6*). The range of reaction temperatures was chosen in agreement with previous experiments (*5*, *6*) and within the range of growth temperatures of hyperthermophiles. The CO gas pressure of 1 bar was chosen as in previous experiments (*5*, *6*) and combined with a reaction time of 10 days (run 1). In other runs, the reaction time was shortened (and product yields increased) by an increase of CO gas pressure. The pH was measured at the end of the reaction. Products in the supernatant were analyzed after freeze-drying by gas chromatography–mass spectroscopy (GC-MS).

α-Hydroxy and α-amino acids as main products (Table 1) constitute ordered series defined by the general formula R-CHA-COOH, where R is H, CH_3, CH_3-CH_2, or HO-CH_2 and A is OH or NH_2. Temperature increase correlates positively with product yield and with the ratio of amino acids to hydroxy acids. The replacement of H_2O by D_2O leads to deuterated products. With ^{13}C-labeled KCN, we discriminated cyano ligands from CO (and, optionally, methylthio) ligands as the carbon source. The resulting isotopomers revealed a rich and complex system of pathways involving all-cyano, all-noncyano, and combined cyano/noncyano ligands, as exemplified by ratios of $^{12}C_3$:$^{13}C_3$ isotopomers for lactate and alanine. The contribution by noncyano pathways correlates positively with a decrease in CO gas pressure and an increase in temperature. This multiplicity of pathways may facilitate metabolic evolution and a stepwise changeover from a Ni-dependent use of CO and/or cyano ligands without energy coupling to a sole use of CO_2 with energy coupling. We also detected α-hydroxy-*n*-valeric acid (run 4, 0.005 μmol), α-hydroxy-*i*-valeric acid (runs 4 and 5, trace amounts), and α-amino-*n*-valeric acid (run 4, trace amount). The progressive chain elongation suggests long-chain α-hydroxy or α-amino acids as primordial lipids.

Added ^{15}N-NH_3 enters the amino acids, which suggests the participation of a pool of ammonia. The replacement of KCN in run 3 by glycine and alanine generated α-hydroxy acids at very low rates. This means that α-amino and α-hydroxy acids are mainly competitive products and, to a minor extent, consecutive products. The detection of glycine amide by high-performance liquid chromatography (HPLC)–MS (*8*) suggests carboxamides as intermediates between CN and COOH groups. The detection of pyruvate (runs 3, 4, 5, and 10) having a similar isotopomer ratio as lactate and alanine suggests α-keto and α-imino groups as intermediates.

Acetate, propionate, and butyrate (in varying isotopomer ratios) have been detected with yields decreasing in that order. The detected ethylene

glycol suggests a pathway via glycol aldehyde, a C_2 sugar. Formate is formed from CO and cyano ligands, with ammonia and formamide as regular by-products.

The reactions are markedly selective. No tar is formed. This may be due to the combination of mild chemical energy and transition metal catalysis. By contrast, the input of harsh physical energy (for example, electric discharges) in the absence of transition metal catalysis results in low-specificity radical reactions with a predominance of tar production (*9*).

The Ni,Fe precipitate may range from amorphous polynuclear structures to nanocrystals with attached clusters. The precipitate has the nominal compositions (before carbonylation and methylthiolation) of $Ni(OH)_2$ + $Ni(CN)_2$ (runs 1 to 5, 7, and 13); $Ni(CN)_2$ (run 6); $Fe(OH)_2$ + $Ni(CN)_2$ (run 8); (Fe,Ni)$(OH)_2$ + (Fe,Ni)S + $Ni(CN)_2$ + $(Ca,Mg)_2Fe(CN)_6$ (runs 9 and 10); $Fe(OH)_2$ + $Ca_2Fe(CN)_6$ (run 11); and $Ni(OH)_2$ (run 12). $Ni(OH)_2$ and $Fe(OH)_2$ are stable against dehydration (*10*) and are insoluble [solubility product constant (K_{sp}) $\cong 10^{-16}$ and 10^{-15}, respectively]. $Ni(CN)_2$ with bidentate cyano ligands is actually $Ni[Ni(CN)_4]$ with $K_{sp} \cong 10^{-9}$ for dissociating into Ni^{2+} and $Ni(CN)_4^{2-}$ (*11*). Together with the stability constants $\beta_4 \cong 10^{30}$ for $Ni(CN)_4^{2-}$ and $K_6 \cong 2 \times 10^8$ for $Fe(CN)_6^{4-}$ (*12*), this implies that the concentration of free dissolved CN^- is effectively zero and that cyano ligands are the reacting species. In the absence of any transition metal (run 14), all cyanide exists as free dissolved CN^- or HCN, but none of the carbon-fixation products are formed. Therefore, our experiments are in sharp contrast to "prebiotic broth" experiments requiring aqueous HCN (*13*) or aqueous CN^- plus ammonia and formaldehyde for Strecker reactions (*14*, *15*).

The redox reactions may be exemplified by the following reaction formulas:

$$CO + H_2O \rightarrow CO_2 + 2H^+ + 2e^- \quad (1)$$

$$2H^+ + 2e^- \rightarrow H_2 \quad (2)$$

$$H_2 \rightarrow 2H^+ + 2e^- \quad (3)$$

$$2CN^- + 2e^- + 3H^+ + 3H_2O \rightarrow HO\text{-}CH_2\text{-}COO^- + 2NH_3 \quad (4)$$

$$3CO + 6e^- + 5H^+ + NH_3 \rightarrow CH_3\text{-}CHNH_2\text{-}COO^- + H_2O \quad (5)$$

where e^- may stand for reduced nickel centers. Besides being a carbon source, CO serves as a primary source of reducing equivalents (reaction 1), akin to the CO dehydrogenase reaction. Hydrogen generated by the reaction (2) is available as a secondary source of reducing equivalents (reaction 3), akin to the hydrogenase reaction. The product CO_2 reacts with $Ca(OH)_2$ to produce calcium carbonate or with $Mg(OH)_2$ to produce basic magnesium carbonate.

A recent theory (*16*) suggests as sites of a Hadean origin intensely fractured, reduced rock in the floors of submerged impact craters, with a wide range of hydrothermal conditions and of rates of hydrothermal quenching. In hot and strongly reducing Hadean magma, fluids have a high molar ratio of CO:CO_2 [for example, 1.5:1 at 1400°C, 10 kbars, and $\log_{10}$ of oxygen fugacity relative to Ni-NiO buffer (ΔNNO $\log_{10}f_{02}$) = 3.5] (*17*). Therefore, Hadean volcanic exhalations must have originated with a correspondingly high equilibrium ratio of CO:CO_2. The equilibrium ratio of CO:CO_2 decreases with decreasing temperature (due to cooling) along the flow path, as long as the composition can equilibrate by the water gas shift reaction (CO + $H_2O \rightarrow CO_2 + H_2$). In the course of this reaction, the reducing agent CO is replaced by H_2, which may also function as a reducing agent according to reaction 3. The water gas shift reaction may be catalyzed by transition metals, or it may be noncatalyzed in the case of high water activity. In one special set of conditions with liquid water of maximum activity, the half-value time for noncatalyzed CO oxidation (CO + $H_2O \rightarrow$ HCOOH $\rightarrow CO_2 + H_2$) has been determined as 2 min at 350°C, 2 weeks at 150°C, and 3 years at 100°C (*18*). Therefore, if the rate of cooling (for example, by intense contact with cold water or ice) is high enough relative to the rate of CO oxidation, the volcanic fluid should be quenched with the result of high-disequilibrium CO and H_2 concentrations (*19*) occurring in many places suitable as the site of emergence of the pioneer organism.

For an aqueous hydrothermal solution of 350°C, an equilibrium concentration of 0.13 mmol of CO per kilogram of solution has been determined with one set of conditions (*18*). Therefore, rapid quenching of hydrothermal fluids from a temperature sufficiently above 350°C down to ~100°C may well result in an aqueous nonequilibrium CO concentration in the vicinity of 0.76 mmol/kg, which has been calculated for the CO gas pressure of 1 bar on the basis of water solubility data (*20*). Moreover, aqueous CO drives the carbonylation of the Ni or Ni,Fe precipitate to form reactive carbonyl complexes. These complexes, however, do not have to form in situ. Rather, under conditions of high pressure and high temperature, CO has been found to mobilize transition metal sulfides by forming carbonyl complexes, which would then be available for subsequent transport (*21*) by the volcanic fluid to a site of an origin by carbonylation reactions at low temperature. The proposal of primordial carbon fixation within a quenched flow of volcanic fluids contrasts with the proposal of primordial carbon-fixation reactions at the interface between aqueous, hydrothermal H_2 and aqueous CO_2 in an acidic ocean

Table 1. Formation of α-hydroxy acids and α-amino acids. M denotes metal and can be either Mg or Ca. d, day; h, hour; nd, product was not detected; tr, trace amount.

Run no.	Base $M(OH)_2$ M (g)	Catalyst/carbon sources* Fe^{2+} (mmol)	Ni^{2+} (mmol)	Na_2S (mmol)	CH_3SNa (mmol)	KCN (mmol)	CO (bar)	T (°C)	Time	pH (final)	Products R-CHA-COOH (μmol)† R	H OH	H NH_2	CH_3 OH	CH_3 NH_2	$HO\text{-}CH_2$ OH	$HO\text{-}CH_2$ NH_2	$CH_3\text{-}CH_2$ OH	$CH_3\text{-}CH_2$ NH_2
1	Ca (1)	0	2	0	0.5	2	1	100	10 d	12.4		0.02	0.03	0.01 (1.8)	0.001 (2)	nd	nd	nd	nd
2	Ca (1)	0	2	0	0.5	2	10	100	5 d	12.4		0.3	0.23	0.01 (30)	0.002 (53)	0.003	0.0008	tr	nd
3	Ca (1)	0	2	0	0.5	2	75	100	2 d	12.5		0.6	0.08	0.10 (75)	0.04 (41)	0.05	0.01	0.005	tr
4‡	Ca (1)	0	2	0	0.5	2	75	100	2 d	12.5		1.1	1.05	0.12	0.09	0.05	0.02	0.02	0.02
5	Ca (1)	0	2	0	0.5	2	75	120	20 h	12.5		2.5	1.7	0.22 (89)	0.15 (93)	0.07	0.03	tr	tr
6	Ca (0.25)	0	1	0	0.5	2	75	80	20 h	10		1.38	nd	0.07 (45)	nd	nd	nd	nd	nd
7	Ca (1)	0	2	0	0	2	75	100	2 d	12.5		0.7	0.4	0.08 (72)	0.02 (88)	0.04	0.02	0.001	tr
8	Ca (1)	1	1	0	0.5	2	75	100	2 d	12.5		0.2	0.04	0.05 (85)	0.0004 (88)	0.02	0.005	0.02	tr
9	Ca (1)	1	1	0.67	0.5	1.33	75	100	2 d	12.5		0.4	0.05	0.10 (41)	0.0006 (82)	nd	nd	nd	nd
10	Mg (0.8)	1	1	0.67	0.5	1.33	75	100	2 d	9		1	0.6	0.20 (43)	0.10 (85)	nd	nd	nd	nd
11	Ca (1)	2	0	0	0.5	2	75	100	2 d	12.5		nd	nd	0.06 (0)	nd	nd	nd	nd	nd
12	Ca (1)	0	2	0	0.5	0	75	100	2 d	12.5		nd	nd	0.02 (0)	nd	nd	nd	nd	nd
13	Ca,Mg§	0	2	0	0.5	2	0	100	2 d	12.8		nd	nd	nd	nd	nd	nd	nd	nd
14	Ca,Mg§	0	0	0	0	2	75	100	2 d	9.6		nd	nd	nd	nd	nd	nd	nd	nd

*Fe^{2+} and Ni^{2+} as sulfates. †The number in parentheses signifies the value of $100{}^{13}C_3/({}^{12}C_3 + {}^{13}C_3)$ as a measure for the ratio of the $^{13}C_3$ isotopomer to the $^{12}C_3$ isotopomer. ‡^{12}C-labeled KCN, D_2O. §Ca(0.45) + Mg(0.5).

(*22*, *23*). Finally, under the conditions of our experiments (below 300°C), the depletion of the chemical potential of CO by the formation of CH_4 and graphite is kinetically inhibited (*19*, *24*).

Cyano ligands of transition metals have been detected at extant volcanic sites (*25*) and may well have been abundant under Hadean conditions. H_2S and methylmercaptan are found in volcanic gases (*26*). Nickel, together with iron, must have been abundant in the Hadean crust and in serpentinized crater floor material. $Ca(OH)_2$ and $Mg(OH)_2$ are formed by precipitation or by serpentinization of ultramafic material (*27*). $Ca(OH)_2$ is also formed by decarboxylation of calcium carbonate to CaO and subsequent hydration (*28*). Therefore, beds of $(Ca,Mg)(OH)_2$ may well have been ubiquitous as a base material for catalyst precipitation in floors of Hadean impact craters and subject to pH zoning (as well as sulfidization zoning and ligand zoning) (*4*).

The conditions of the present experiments are closely related to the conditions of previous studies in the context of a chemoautotrophic origin of life (*3*) and notably to the formation of methylmercaptan (*29*), to nitrogen fixation (*30*), to the formation of COS (*5*), and to the involvement of COS as a source for energy (*6*) and carbon (*2*). Therefore, all these reactions could cooperate with the newly found reactions in a locally and temporally coherent manner at volcanic, hydrothermal sites or along volcanic, hydrothermal flow channels. Our results free the hydrothermal origin-of-life debate from a narrow focus on Fischer-Tropsch reactions and obviate considerations (*31*) of combining the theory of a prebiotic broth of amino acids (*9*) with the theory of a chemoautotrophic origin of life.

It has been suggested that the formation of amino acids at hydrothermal sites would be under the thermodynamic control of metastable equilibria (*32*). Our results are consistent with kinetic control, because the α-amino acids are thermodynamically unstable and convert slowly into α-hydroxy acids; glycine is the most favored α-amino acid, whereas, under thermodynamic control, glycine should be least favored (*32*); yields of α-hydroxy and α-amino acids decrease with increasing carbon skeletons and with an increasing number of mechanistic steps, as expected from kinetically controlled reactions; yields and product ratios vary with the catalyst system. Such kinetic control is a necessary condition for the involvement of our reactions in the autocatalytic (reproductive) metabolism of a pioneer organism. Moreover, kinetic control makes room for an increase of catalytic activity by evolution from very low de novo rates to rather high autocatalytic rates and for the possibility of chiral symmetry breaking by autocatalytic ligand feedback.

This discussion concludes with the evolutionary context of our results. α-Hydroxy and α-amino acids are chelating ligands for transition metals. The synthesis of these compounds under presumptive Hadean, volcanic, hydrothermal conditions therefore supports the notion that the earliest mechanism of reproduction and evolution was based on positive (autocatalytic) feedback (*1*–*4*), whereby certain synthetic products led to ligand-accelerated transition metal catalysis (*3*, *4*) that greatly increased the rates of the synthetic reactions, the activities of their products, and the spectrum of feedback possibilities, with an eventual emergence of metalloenzymes.

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33. This work was funded by Deutsche Forschungsgemeinschaft (grants WA-983/1-4 and WA-983/2-1,2). We thank A. Bacher for providing the laboratory facilities and for material support, B. Cordes for HPLC-MS analysis, C. Schwarz for technical assistance, and four anonymous referees for improvements of the manuscript.

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5799/630/DC1
Materials and Methods

5 June 2006; accepted 22 September 2006
10.1126/science.1130895

Interface Mobility from Interface Random Walk

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Computational studies aimed at extracting interface mobilities require driving forces orders of magnitude higher than those occurring experimentally. We present a computational methodology that extracts the absolute interface mobility in the zero driving force limit by monitoring the one-dimensional random walk of the mean interface position along the interface normal. The method exploits a fluctuation-dissipation relation similar to the Stokes-Einstein relation, which relates the diffusion coefficient of this Brownian-like random walk to the interface mobility. Atomic-scale simulations of grain boundaries in model crystalline systems validate the theoretical predictions and highlight the profound effect of impurities. The generality of this technique, combined with its inherent spatiotemporal efficiency, should allow computational studies to effectively complement experiments in understanding interface kinetics in diverse material systems.

Engineering material microstructures for a desired combination of properties (*1*–*4*), whether mechanical, transport, or chemical, hinges upon our ability to control final microstructural parameters such as crystal fraction, grain size, texture, and interface type. Processing routes commonly used in industry result in evolution of the interfacial network, as in solidification (*5*) and more general phase transformations (*6*); recovery and recrystallization during metal forming (*7*); and grain/domain evolution in polycrystals (*8*), multiphase materials (*6*), and composites (*4*). In each case, it is the motion of interfaces that sets the evolution rate and final form of the interfacial microstructure.

Structure and environment dependence of interface kinetics is captured through the interface mobility M, a parameter that relates the interface normal velocity v to the driving force (pressure) p.

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Current understanding is restricted to near equilibrium, where linear gradient approximations predict a linear relation, i.e., $v = Mp$ (*9*, *10*). In systems where the motion is activated, the mobility increases exponentially with temperature T, i.e., $M \propto \exp(-Q/k_BT)$, where Q is the energy required to activate the rate-limiting event(s) associated with macroscopic interface motion and k_B is the Boltzmann constant. Efforts aimed at extracting mobility have focused on the motion of individual interfaces. The motion of crystalline interfaces has been investigated through the use of several driving forces (*8*, *11*)—interfacial curvature, bulk driving forces such as elastic and plastic strains, stored energy of deformation, electromagnetic fields, and thermochemical gradients (*12*–*14*). Quantitative comparisons between experiments and atomic-scale computer simulations have revealed large discrepancies that have been difficult to reconcile, even for the relatively simpler case of grain boundaries (*11*, *15*–*20*). In particular, the experimental activation energies for migration are considerably higher. The difference is usually attributed to the additional drag exerted by impurities that are invariably present in the experiments. In general, it is believed that even minute impurity levels substantially retard interface motion (*7*, *8*, *11*, *17*, *21*).

The computations are performed at extremely high driving forces such that the interface is driven far from equilibrium. This is a shortcoming because the assumptions central to activated kinetics may no longer be true; the linear gradient approximation may break down and the migration mechanism may itself change qualitatively. It is quite possible that the mobility may develop a driving force dependence. Additionally, the extent of impurity drag is no longer accurate because it is based on comparisons between experiments and computations, an issue whose resolution is of paramount importance to industrial processing routes. Extending the computational techniques to more realistic driving forces is problematic. These studies are performed using deterministic molecular dynamics (MD) simulations with appropriate interatomic interactions, because the interface motion is due to kinetic mechanisms set at the atomic scale (*16*–*20*). However, these simulations are limited to tens of nanoseconds; thus, in order to get statistical meaningful data, the interface must be forced to undergo appreciable migration within a short time interval, i.e., the driving force must be very large.

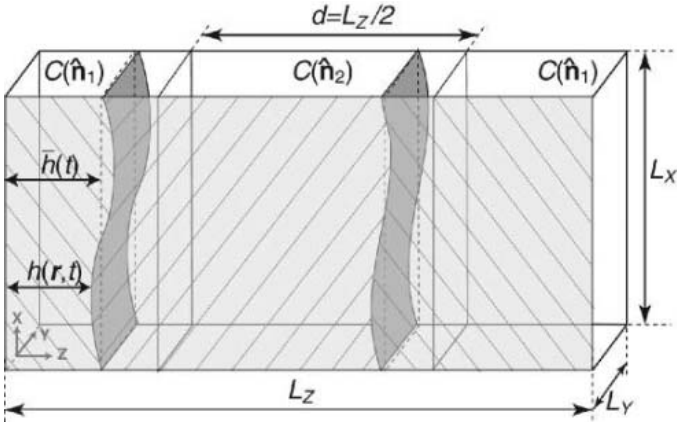

Fig. 1. Schematic of the fully periodic computational cell $\{L_X, L_Y, L_Z\}$ used for extracting grain-boundary mobility. The two fcc crystals $C(\hat{n}_1)$ and $C(\hat{n}_2)$ are misoriented by tilting them equally about the Y direction, which corresponds to the ⟨111⟩ crystal direction. The symmetry of the tilt is indicated by the hatched lines. The initial position of the boundary (solid lines, unshaded), the fluctuating profile $h(\mathbf{r}, t)$ (shaded), and the computed average $\bar{h}(t)$ (dotted, unshaded) are also shown.

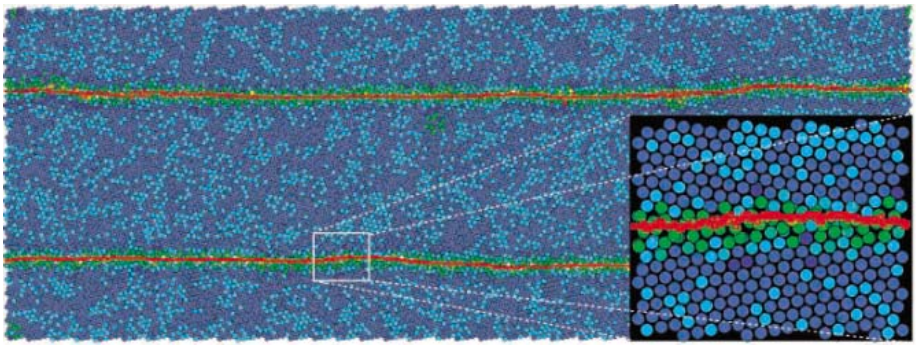

Fig. 2. Atomic snapshot of the Lennard-Jones computational cell viewed along the Y direction. The color reflects the interaction energy—green color indicates high-energy states. (**Inset**) A close-up picture of two crystals abutting the grain boundary. The superposed red dotted curve is the result of the algorithm used to dynamically identify the interface position (*24*) (fig. S1).

We present a computational method that yields absolute mobilities of flat interfaces in the zero driving force limit. The methodology still involves deterministic atomic-scale computations, but they are performed in the absence of a driving force. Studies on flat interfaces are ideal because they permit full control over all degrees of freedom, enabling exploration of the effect of interface structure and environment. Such simulations have been performed for grain boundaries by means of bulk driving forces, albeit in the high driving force limit. One exception is a recent study that extracts the mobility of a grain boundary (*22*) by using a capillary fluctuation method developed for solid-liquid interfaces (*23*). However, this method requires large interface shape fluctuations and thus breaks down near singular orientations where these fluctuations are suppressed by a diverging interface stiffness. In contrast, we circumvent this limitation by focusing on the random walk of the mean interface position. We apply this methodology to an initially flat grain boundary in face-centered-cubic (fcc) bicrystals based on a model pairwise Lennard-Jones (LJ) potential, and then a more sophisticated embedded-atom-method (EAM) potential for aluminum (*24*). The technique is general because it can be easily extended to mobile interfaces in multicomponent, multiphase material systems.

In the continuum limit, the normal interface velocity v of a fluctuating interface is due to capillary driving forces $p = \kappa_\gamma$ and a bulk Langevin force η associated with the intrinsic thermal fluctuations,

$$v = M(\kappa_\gamma + \eta) \qquad (1)$$

The capillary force is simply the mean interface curvature multiplied by its stiffness, i.e., $\kappa_\gamma = \Gamma\kappa$, where the stiffness follows from the orientation (ϕ) dependence of the interface free energy, $\Gamma = \gamma + \gamma_{\phi\phi}$ (*25*). We choose, without loss in generality, the interface to be perpendicular to the Z direction. The bulk forces due to the thermal noise are expected to be uncorrelated in space and time and can be expressed as $\eta \equiv \eta(\mathbf{r}, t)$, where the coordinate $\mathbf{r} = (x, y)$ is restricted to the interfacial plane. Denoting the interface height profile as $h(\mathbf{r}, t)$ and working under the small slope approximation ($h_x << 1$, $h_y << 1$), the interface velocity (Eq. 1) can now be expressed in terms of the height profile, $v = h_t = M[\Gamma(h_{xx} + h_{yy}) + \eta]$. Integrating both sides of this relation in space and time, and assuming a fully periodic interface typically used in most computational cell geometries, yields mean square displacement $\langle \bar{h}^2 \rangle = Dt$ with the diffusion coefficient

$$D = \frac{2Mk_BT}{A} \qquad (2)$$

where A is the area of the interface plane within the computational cell (*24*). Thus, the average position of the interface performs a classical random walk such that the variance $\langle \bar{h}^2 \rangle$

increases linearly with time and the rate of increase yields the absolute interface mobility. The above fluctuation-dissipation relation is the direct analog for an interface of the classic Stokes-Einstein relation $D = k_B T/(6\pi R\tilde{\eta})$ for the diffusion coefficient of a Brownian particle. In this analogy, the interface can be simply interpreted as an effective particle of radius R, proportional to the interface area, performing a random walk constrained to one dimension in a fluid of viscosity $\tilde{\eta}$, now inversely proportional to the interface mobility.

As validation, we perform classical MD simulations of an initially flat grain boundary in a fcc lattice $\{L_X, L_Y, L_Z\}$ (Fig. 1). We gain efficiency by using a ribbon-shaped grain boundary geometry as the computational cell size is substantially reduced (~40,000 atoms). The bicrystal separates two crystals labeled $C(\hat{\boldsymbol{n}}_1)$ and $C(\hat{\boldsymbol{n}}_2)$ with prescribed orientations $\hat{\boldsymbol{n}}_1$ and $\hat{\boldsymbol{n}}_2$. A ⟨111⟩ symmetric tilt grain boundary is chosen for the study; the two crystals are tilted with respect to each other about the ⟨111⟩ axis such that it lies along the resultant boundary plane, and the total misorientation θ is distributed equally about the boundary plane, i.e., $\cos^{-1}(\hat{\boldsymbol{n}}_1 \cdot \hat{\boldsymbol{x}}) = \cos^{-1}(\hat{\boldsymbol{n}}_2 \cdot \hat{\boldsymbol{x}}) = \theta/2$. We restrict ourselves to the θ = 38.2°, high-symmetry misorientation (*11*). The choice is additionally motivated by the fact this is a well-studied grain boundary system, permitting comparisons with previous experimental and computational studies.

Equilibrium MD simulations are performed at high temperatures, $0.9T_m$ for the LJ system and $0.8T_m$ (750 K) for the EAM-Al system, where T_m is the bulk melting point (*24*). Figure 2 shows an atomic-plot of the LJ bicrystal system at an intermediate time step. The fluctuations along the grain boundary normal are evident. Similar fluctuations and appreciable boundary plane displacements are also observed in the EAM-Al bicrystal simulations (movie S1). The average grain boundary position $\bar{h}(\mathbf{r}, t)$ is determined from the height profiles dynamically computed at discrete time slices (*24*) (fig. S1). The profile is averaged along the X and Y directions in order to extract the average position $\bar{h}(t)$. The ensemble variance is calculated by executing multiple simulations in parallel (*24*). Spatial correlations can arise due to elastic interactions between the two grain boundaries within the computational cell, mainly due to insufficient spacing between the grain boundaries. Plots of the average height profile as a function of simulation time visually confirm the absence of notable correlations, both across and within the simulations (fig. S2). A more rigorous check is to see if the evolution of the average interface position $\bar{h}(t)$ maintains a normal (Gaussian) distribution within each time interval. Such a plot is shown in Fig. 3 for the EAM-Al simulations. The distribution is clearly Gaussian at each of the four time intervals shown, with the width and the height evolving as expected. The fact that the distribution is symmetrical about its peak demonstrates that there is negligible interaction between the two interfaces in our periodic cell, which is an essential requirement for extracting the intrinsic mobility of a single interface by the present method. In addition, the Gaussian nature of the distribution provides further validation of the predicted random walk behavior of the interface from the fluctuation analysis. Similar behavior is also observed in the LJ simulations.

Temporal evolution of $\langle \bar{h}^2 \rangle$ extracted from both sets of simulations is plotted in Fig. 4. The LJ simulation plot is based on fits to Al parameters, henceforth referred to as LJ-Al (*24*). The variation is linear as predicted by the theory and yields the absolute mobilities: $M = 7.7 \pm 0.3 \times 10^{-8}$ and $M = 4.4 \pm 0.05 \times 10^{-7}$ m^4 J^{-1} s^{-1} for the LJ-Al and EAM-Al simulations, respectively. The efficiency of this technique can be gauged by the fact that mean displacements on the order of an interatomic distance and ~20 independent runs are sufficient to extract a convergent slope. To verify if the mobility we extract is indeed that associated with long-range interface motion, we performed longer simulations (350 ps) at a higher temperature (900 K). In these simulations, the mean interface position displaces by several interatomic distances. Moreover, the rate of increase of $\langle \bar{h}^2 \rangle$ (the slope) becomes time independent for $t > 100$ ps.

Although the computational cell is fully periodic, the ribbon-shaped grain boundary geometry can potentially introduce dimensional artifacts in the fluctuation spectra. Larger simulation cells (up to a factor of 2 along each direction, including square-shaped grain boundaries) reveal that although the fluctuations in the height profile decrease with the cell size, the rate of increase of the variance remains unchanged, i.e., the extracted mobility is cell-size independent. Although the LJ-Al simulations are performed at a higher temperature, the mobility is almost an order of magnitude smaller. This large difference indicates that neglecting many-body effects leads to a sizable underestimation in the extent of grain boundary kinetics, highlighting the high degree of sensitivity of interface kinetics to the accuracy of the atomic-scale interactions.

To put our results in perspective, Table 1 lists relevant previous experimental and computed mobilities in several metal systems (Al, Cu, Ni, Ag, Pb, and Au), under similar conditions and various driving forces. To facilitate comparison, the LJ results have been parameterized for these metal systems (*24*). In the case of bicrystal simulations in Al (rows 1 to 4), the comparisons are particularly well suited because the previous studies have been performed on the exact same grain boundary system, i.e., a ⟨111⟩ 38.2° symmetric tilt boundary. Both EAM and LJ comparisons (rows 1 and 3 and rows 2 and 4) reveal that the large driving force mobilities are close to an order of magnitude lower, suggesting that the

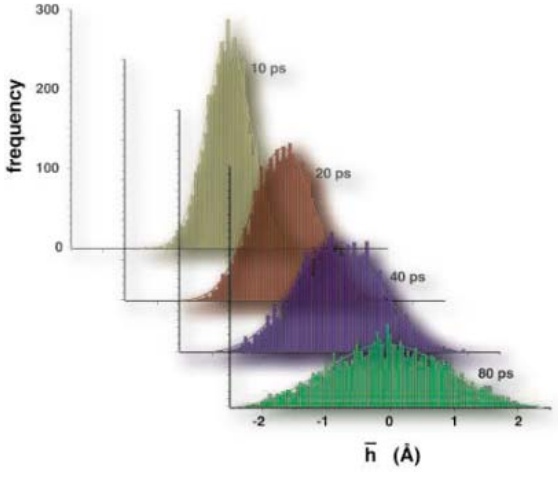

Fig. 3. Distribution of the average interface position $\bar{h}(t)$ in the EAM-Al simulations, with respect to the initial position $\bar{h}(0) = 0$ and at four time intervals t = 10, 20, 40, and 80 ps. Gaussian fits of the form $f = A \exp(-\alpha \bar{h}^2)$ are also shown, where the constants A and α are measures of the height and width of the distribution, respectively.

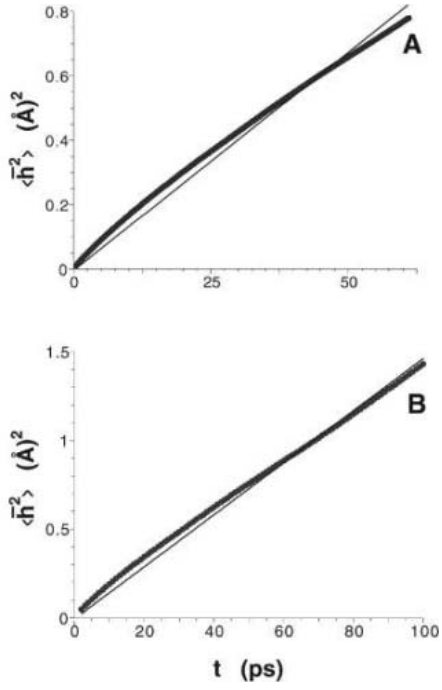

Fig. 4. Temporal evolution of the variance $\langle \bar{h}^2 \rangle$ for the (**A**) LJ-Al and (**B**) EAM-Al simulations. Linear fits of the form $\langle \bar{h}^2 \rangle = Dt$ are also shown.

Table 1. Grain-boundary mobilities extracted at and around the ⟨111⟩ θ = 38.2° misorientation and for temperatures 0.8 to 0.9T_m. In some cases, we have extrapolated the reported temperature dependence. Also, due to the lack of data in some metals (Cu and Ni), we have used data on average mobilities of several high-angle grain boundaries with varying structure and driving forces.

	Material system [geometry, θ (°)]	Temperature [T (°K)]	Driving force [p (Pa)]	Mobility [M (m^4 J^{-1} s^{-1})]
1	EAM-Al, flat, 38.2	750 (0.80T_m)	Random walk, $p \sim 0$	4.4×10^{-7}
2	LJ-Al, flat, 38.2	840 (0.90T_m)	Random walk, $p \sim 0$	7.7×10^{-8}
3	EAM-Al, flat, 38.2	800 (0.86T_m)	Synthetic, $p \sim \times 10^8$	6.0×10^{-8} (*20*)
4	LJ-Al, flat, 38.2	840 (0.90T_m)	Deformation, $p \sim \times 10^7$	1.3×10^{-8} (*27*)
5	EAM-Al, half-loop, 38.2	750 (0.80T_m)	Curvature, $p \sim \times 10^7$	1.0×10^{-6} (*19*)*
6	Al (6N), flat, 35.0	750 (0.80T_m)	Stress, $p \sim \times 10^4$	2.1×10^{-11} (*28*)
7	Al (6N), flat, 40.0	750 (0.80T_m)	Deformation, $p \sim \times 10^5$	8.3×10^{-9} (*29*)†
8	Al (4N), flat, 40.0 (high angle)	750 (0.80T_m)	Deformation, $p \sim \times 10^5$	5.0×10^{-9} (*30*)†
9	Al (2N), flat, 40.0	663 (0.71T_m)	Deformation, $p \sim \times 10^5$	1.3×10^{-11} (*31*)†
10	Al (2N), flat, 40.0	888 (0.95T_m)	Deformation, $p \sim \times 10^5$	1.8×10^{-10} (*32*)†
11	Al (2N), flat, 40.0	773 (0.83T_m)	Deformation, $p \sim \times 10^5$	2.8×10^{-11} (*33*)†
12	Al (2N), flat, 40.0	750 (0.80T_m)	Deformation, $p \sim \times 10^5$	1.2×10^{-12} (*34*)†
13	Al (2N), half-loop, 38.2	758 (0.81T_m)	Curvature, $p \sim \times 10^3$	5.0×10^{-9} (*11*)*
14	Al (6N), quarter-loop, 38.2	758 (0.81T_m)	Curvature, $p \sim \times 10^2$	3.5×10^{-9} (*11*)*
15	Al (6N), half-loop, 36.8	750 (0.80T_m)	Curvature, $p \sim \times 10^3$	1.5×10^{-9} (*35*)*
16	Al (6N), wedge, 40.0	750 (0.80T_m)	Curvature, $p \sim \times 10^2$	2.7×10^{-10} (*36*)*
17	LJ-Cu, flat, 38.2	1221 (0.90T_m)	Random walk, $p \sim 0$	3.5×10^{-8}
18	Cu (3N), ⟨θ⟩ (high angle)	1221 (0.90T_m)	Deformation, $p \sim \times 10^4$	8.2×10^{-8} (*37*)†
19	LJ-Ni, flat, 38.2	1555 (0.90T_m)	Random walk, $p \sim 0$	3.0×10^{-8}
20	EAM-Ni, flat, 38.2	1400 (0.81T_m)	Fluctuations, $p \sim 0$	1.2×10^{-7} (*22*)
21	Ni (5N), ⟨θ⟩ (high angle)	1555 (0.90T_m)	Deformation, $p \sim \times 10^6$	5.0×10^{-9} (*38*)
22	LJ-Pb, flat, 38.2	540 (0.90T_m)	Random walk, $p \sim 0$	6.5×10^{-8}
23	Pb (6N), flat, 36-42	540 (0.90T_m)	Deformation, $p \sim \times 10^3$	1.1×10^{-8} (*39*)†
24	LJ-Ag, flat, 38.2	1111 (0.90T_m)	Random walk, $p \sim 0$	4.2×10^{-8}
25	Ag (4N), flat, 35.0	923 (0.75T_m)	Deformation, $p \sim \times 10^2$	1.5×10^{-10} (*40*)†
26	LJ-Au, flat, 38.2	1203 (0.90T_m)	Random walk, $p \sim 0$	2.7×10^{-8}
27	Au (4N), flat, 30.0	1203 (0.90T_m)	Deformation, $p \sim \times 10^2$	5.0×10^{-9} (*41*)†

*Curved boundaries span several interface inclinations and therefore these studies yield inclination-averaged reduced mobilities, $\langle M^* \rangle = \langle M\Gamma \rangle$. The reported absolute mobilities in simulations are overestimates because they are based on extracted boundary enthalpies. The experimental values assume a stiffness value Γ = 0.5 J/m^2. †These studies monitor a recrystallized grain of a known orientation growing into a deformed matrix.

mobility is indeed sensitive to the driving force. It is unclear if this dependence is due to the physical nature of the driving force, which differs in each comparison, or its extent alone. The mobility extracted from curvature studies (row 5) is closer in magnitude. However, the comparison is weak because these values are derived from inclination-averaged reduced mobilities spanning several inclinations as well as an assumed value of the average interface stiffness, an inherent limitation in all curvature-driven studies.

The experimental values show an overall decreasing trend with the impurity levels (rows 6 to 16) and are at least two orders of magnitude smaller, irrespective of the nature of the driving force. Our mobility values are appreciably higher than those in previous simulations, indicating that the effect of impurities in the low-velocity regime is much more dramatic than previously thought (*17*). Comparisons between experimentally extracted mobilities in other metal systems and the parametrized LJ results further reinforces this conclusion, where we have assumed that the LJ values underestimate the mobility by at least an order of magnitude (*26*). Thus, this behavior appears to be a general trend. A more accurate estimate of the extent of the impurity drag effect requires extraction of activation energies, with and without impurities and as a function of interface degrees of freedom. The length- and time-scale efficiencies offered by our methodology, suitably modified to account for the presence of impurities, are perhaps the only viable solution for quantifying this effect at the atomic scale, while making contact with experiments in a wide range of interfacial systems.

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42. The study was partially funded by U.S. Department of Energy (DOE)–sponsored Computational Materials Science Network (CMSN) on "Fundamentals of Dirty Interfaces: From Atoms to Alloy Microstructures." M.U. also acknowledges support from Structural Metallics Program, Office of Naval Research, U.S. Department of Defense (DOD), Award N00014-06-1-0207 titled "Particle Strengthened Interfaces," and Alcoa Technical Center. A.K. was also supported by DOE grant DE-FG02-92ER45471. This research used resources of the Naval Oceanographic Office Major Shared Resource Center, supported by the U.S. DOD, and the National Energy Research Scientific Computing Center, which is supported by the Office of Science of the U.S. DOE under Contract DE-AC02-05CH11231.

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30 June 2006; accepted 15 September 2006
10.1126/science.1131988

X-ray–Induced Dissociation of H_2O and Formation of an O_2–H_2 Alloy at High Pressure

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When subjected to high pressure and extensive x-radiation, water (H_2O) molecules cleaved, forming O–O and H–H bonds. The oxygen (O) and hydrogen (H) framework in ice VII was converted into a molecular alloy of O_2 and H_2. X-ray diffraction, x-ray Raman scattering, and optical Raman spectroscopy demonstrated that this crystalline solid differs from previously known phases. It remained stable with respect to variations in pressure, temperature, and further x-ray and laser exposure, thus opening new possibilities for studying molecular interactions in the hydrogen-oxygen binary system.

H_2O forms at least 15 stable (*1*) and metastable crystalline (*2*–*5*) and amorphous ices (*6*–*9*). Its rich phase diagram displays a range of exotic behavior such as symmetric hydrogen bonds (*10*–*12*), superionic ice (*13*, *14*), and multiple critical points (*15*, *16*). We excited H_2O with high-energy x-radiation to access a larger portion of the energy landscape at high pressure. Although at ambient pressure x-rays are known to produce metastable free radicals in molecular systems or to induce stable reactions by overcoming kinetic-energy barriers, documented examples of x-ray–induced transitions at high pressure have been extremely rare.

We observed the x-ray– and pressure-induced cleaving of H_2O in an oxygen K-edge study with a high-pressure x-ray Raman scattering (XRS) technique (*5*, *17*–*19*) that requires long exposure of moderately high energy (~10-keV) x-radiation. For oxygen bonded with hydrogen in H_2O, the K-edge XRS spectra are dominated by a cluster of peaks around 540 eV, as shown in dense water below 0.9 GPa, ice VI between 1 and 2 GPa, and ice VII just above 2 GPa (Fig. 1). At pressures above 2.5 GPa, however, x-radiation induced pronounced, irreversible changes in the XRS spectra. A distinctive, sharp peak appeared at 530 eV that was characteristic of O–O bonding in O_2 and grew with time, reaching a plateau after 6 hours of exposure to the incident x-ray beam (Fig. 1). The plateau intensity increased with increasing pressure, and at 15.3 GPa, the height of the 530-eV peak matched that of the main 540-eV multiplet. We observed the reaction independently at the Advanced Photon Source (APS) and at SPring-8 during high-pressure XRS measurements of H_2O (Fig. 1). Visually, the sample changed from colorless to light brown after the conversion (Fig. 2A). Optical Raman scattering (ORS) measurements showed intense, characteristic H_2 and O_2 vibrons and a diminished H_2O signal (Fig. 3), clearly demonstrating the dissociation of H_2O molecules and the recombination into O_2 and H_2 molecules.

The resultant O_2 and H_2 molecules did not exist in the known high-pressure phases of hexagonal close-packed (hcp)–H_2 and ε-O_2 but formed an alloy consisting of both molecular O_2 and H_2. To better understand this material, we varied x-ray energy and exposure time, interval between exposure and measurement, pressure, and temperature, and we studied the samples with ORS and x-ray diffraction (XRD). At 17.6 GPa after x-radiation, the OH vibrational modes around 3000 cm^{-1} became diminishingly weak and exhibited a different shape in comparison to that of ice VII (Fig. 3), indicating that the H_2O molecules had mostly cleaved, leaving only a minor component in the new O_2–H_2 alloy. We can rule out the hcp-H_2 and ε-O_2 phases on the basis of their characteristic ORS spectra. The intense $Q_1(1)$ H_2 molecular vibron at 4304 cm^{-1} (Fig. 3) is 59 cm^{-1} above the $Q_1(1)$ of pure hcp-H_2 (4245 cm^{-1}) (*20*). The weak side peak at 4236 cm^{-1} indicates a small amount (<5%) of H_2 in a different site or possibly in a new secondary phase. The H_2 molecular excitations [$S_0(0)$, $S_0(1)$, and $S_0(2)$ at 360, 610, and 847 cm^{-1}, respectively] are characteristic of freely rotating H_2 molecules. The O_2 ORS vibron frequency (1577 cm^{-1}) is similar to that of ε-O_2 (*21*, *22*), but the intense, low-frequency, librational peaks

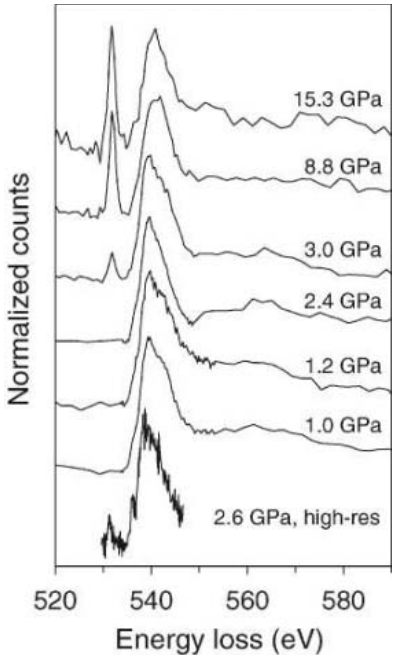

Fig. 1. XRS of the H_2O sample at high pressure after 12 hours of irradiation. The bottom spectrum at 2.6 GPa was measured at beamline BL12XU, SPring-8, by means of 9.886-keV x-radiation with high-energy resolution (300 meV). All other spectra for 1.0, 1.2, 2.4, 3.0, 8.8, and 15.3 GPa were measured with 9.687-keV x-radiation at beamline 13-IDC, APS, ANL, with 1-eV resolution.

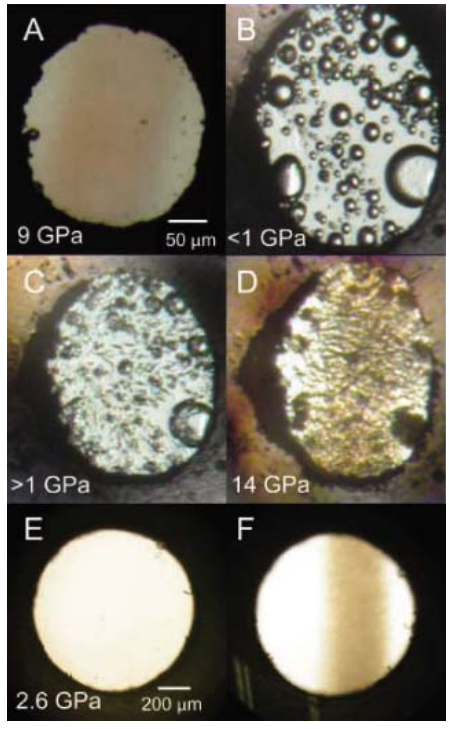

Fig. 2. Photomicrographs of two diamond anvil cell samples. The top four panels were taken at 13-IDC, APS, ANL; the bottom two panels were taken at BL12XU, SPring-8. (**A**) Sample after XRS measurement at 8.8 GPa. The light brown streak through the middle of the sample shows the portion irradiated by the x-ray beam. A small ruby ball on the left edge of the gasket was used for pressure calibration. (**B**) After the release of pressure to below 1 GPa, bubbles of O_2 and H_2 formed. (**C**) Bubbles collapsed upon the increase of pressure as the H_2 and O_2 were incorporated into the crystalline sample. (**D**) Sample after XRS measurement at 15.3 GPa. (**E**) Sample before and (**F**) after x-ray exposure at 2.6 GPa.

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at 123 and 272 cm^{-1} are substantially lower in frequency than the characteristic ν_{L1} and ν_{L2} modes of ε-O_2 at 155 and 360 cm^{-1}, respectively, indicating that this phase is not ε-O_2. The observation of a single O_2 vibron and a predominant H_2 vibron is consistent with a new alloy conserving the O_2:H_2 ratio of approximately 1:2 [i.e., $(O_2)(H_2)_2$], although we cannot rule out the possibility of a minor secondary phase with a different O_2:H_2 ratio, corresponding to the weak H_2 side peak at 4236 cm^{-1}.

The H_2 vibron stiffening in mixed crystals has been used extensively to reveal information on the matrix isolation and intermolecular interactions of H_2 (*23*, *24*). The vibron turnover of pure hcp-H_2 (*20*) shifts to higher pressure in the mixed crystals, and the effect increases with increasing molecular fraction of other molecules, such as Ne, HD, and D_2 (*23*, *24*). In the transformed material, the main H_2 vibron shows substantial stiffening, which suggests the presence of a large amount of O_2 (Fig. 3). The pressure shifts of the ORS O_2 librational peaks and H_2 vibrons are shown in Fig. 4 and are compared with corresponding peaks of hcp-H_2 and ε-O_2. Similar pressure dependence and constant offset of ORS peaks of the present alloy with respect to the pure endmembers indicate that these peaks have similar origins but different matrices' effects.

We conducted XRD studies of the H_2–O_2 alloy at beamline 16-IDB of the High Pressure Collaborative Access Team (HPCAT), APS, Argonne National Laboratory (ANL). Sharp powder diffraction rings indicate that the alloy is a well-crystallized solid. Its diffraction pattern (Fig. 5) shows some similarity to, but does not exactly fit, ε-O_2 (*25*–*27*). For instance, they both have a multiplet group between 2 and 2.4 Å, and the alloy has a doublet near 3.4 Å, where ε-O_2 has a singularly strong peak (*25*). At this point, it is premature to present a definitive crystal structure or unit cell based on only 10 powder XRD lines. The *d*-spacings of the alloy, ε-O_2, and ice VII vary similarly with pressure, implying that all have similar compressibilities (Fig. 6).

Once synthesized and kept at high pressure, the new phase was stable with respect to laser exposure, further x-radiation, and being stored for time intervals of more than 120 days. Bubbles of O_2–H_2 gaseous mixture (identified by ORS) were released from the solid when the pressure was reduced below 1 GPa (Fig. 2B). When these bubbles were compressed to high pressures and irradiated with x-rays again, they re-formed the new alloy (Fig. 2D). Formation of this material has thus been approached from both directions, starting with H_2O and with an O_2–H_2 mixture. Heated in a diamond anvil cell, the alloy is stable up to 700 K at 15 GPa. At higher temperatures, this material reverts to ice VII near melting.

Partial dissociation of ice VII was previously observed by Lin *et al*. (*28*) in high pressure–high temperature experiments of H_2O, but the reaction conditions and products were different. At high temperature and without x-radiation, Lin *et al*. detected a minor amount of ε-O_2 (but no H_2) as a result of hydrogen loss to the metal gasket. The present observation also differs from results for hydrogen peroxide (H_2O_2), which when compressed, first transforms to a high-pressure phase (H_2O_2-II) and then at high pressures decomposes to H_2O + O_2, without the production of any H_2 molecules (*29*). Our alloy does not match the $(O_2)_3(H_2)_4$ phase reported at 7.5 to 10 GPa (*30*), which was unstable and combusted during x-radiation. Moreover, the O_2 and H_2 ORS vibrons of the $(O_2)_3(H_2)_4$ phase agree with those of ε-O_2 and hcp-H_2, respectively, and thus differ from those of our alloy.

The kinetic stability of the new material implies that there is an energy minimum separated from ice VII by a large energy barrier. The barrier may be too high to cross by thermal excitation alone, because it has not been observed in high pressure–high temperature experiments up to 1000 K (*14*, *28*), which is equivalent to 0.08 eV. The ~10-keV x-rays that we used provide access to a large range of local energy minimum states, including both ground and trapped excited electronic states of O_2 and H_2. It may be puzzling why this new phase was not discovered earlier in previous XRD studies of high-pressure ices. We conducted a reconnaissance study using several different monochromatic x-ray

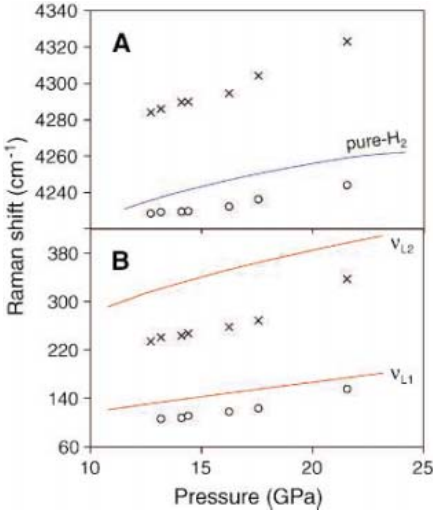

Fig. 4. Pressure dependence of ORS shift for the O_2–H_2 alloy. (**A**) Symbols show the positions for the H_2 vibron doublet. Blue line shows the position for the pure H_2 vibron (*20*). (**B**) Symbols show the positions of the low frequency modes. Red lines show the librational modes of ε-O_2 (*21*, *22*).

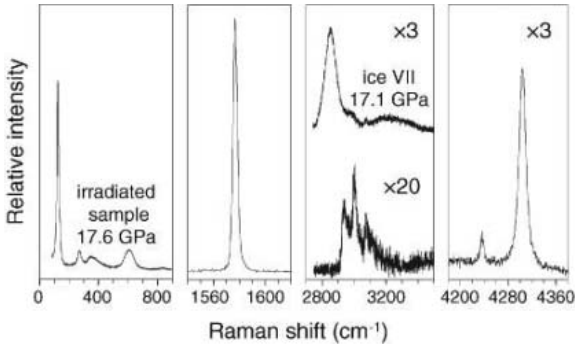

Fig. 3. ORS measurements of an irradiated sample at 17.6 GPa. The ORS measurements of an unirradiated ice VII sample at 17.1 GPa are shown for comparison. All measurements were based on the same exposure time; intensity scaling is noted by multiplication factors. The Raman modes in the sample were excited using Ar^+ ion laser radiation at 488 nm.

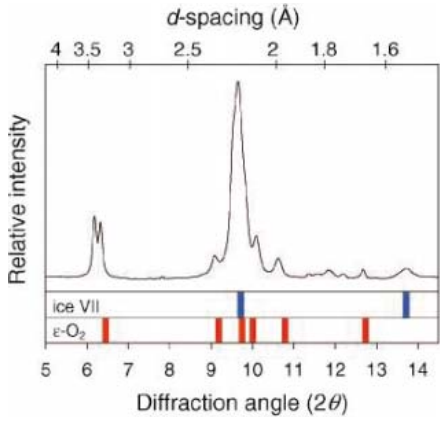

Fig. 5. Integrated XRD pattern of the irradiated sample at 15.3 GPa, where wavelength λ = 0.36819 Å. Comparisons for expected peak positions at 15.3 GPa for ε-O_2 (*21*, *26*) and ice VII (*31*) at 15.3 GPa are shown as red and blue bars, respectively.

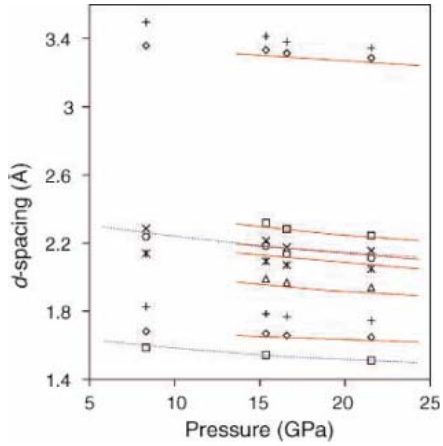

Fig. 6. Pressure dependence of *d*-spacings for reflections from the new O_2–H_2 alloy. Solid red and dotted blue lines show the pressure dependence for ε-O_2 (*21*, *26*) and ice VII (*31*), respectively.

energies of 9.687, 9.886, 14.414, and 33.678 keV. The x-ray–induced reaction in ice VII was most effective with 9.687- and 9.886-keV x-radiation, which are absorbed readily by H_2O; was less effective with 14.414-keV x-radiation; and was not observed with 33.678-keV high-energy x-radiation, which passed through H_2O without adequate absorption. High-pressure synchrotron XRD studies typically use high-energy x-radiation above 20 keV with short exposure times of seconds to minutes; this would be insufficient to induce the reaction. On the other hand, low-energy x-radiation below 12 keV would be largely absorbed by the diamond anvils and are seldom used for XRD studies. In our experiments, the ~10-keV x-rays pass through the low-absorbance Be gasket and provide optimal conditions for inducing the reaction.

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32. We thank S. Ghosh for assistance with the XRS at APS; N. Hiraoka, I. Jarrige, H. Ishii, and C. C. Chen for assistance with the XRS at SPring-8; S. Sinogeiken for assistance with the ORS; and M. Somayazulu and A. Levedahl for assistance with resistive heating measurements. The NSF–Division of Materials Research (DMR-0508988), NSF–Division of Earth Sciences (EAR) Petrology and Geochemistry, NSF-EAR Geophysics, and NSF-EAR Instrumentation and Facility Programs provided financial support, and HPCAT provided synchrotron beam time. GeoSoilEnviro Consortium for Advanced Radiation Sources is supported by the NSF-EAR (EAR-0217473), U.S. Department of Energy (DOE)–Geosciences (DE-FG02-94ER14466), and State of Illinois. HPCAT is supported by the DOE–Basic Energy Sciences (BES), DOE–National Nuclear Security Administration, Carnegie DOE Alliance Center, NSF, Department of Defense–Tank-Automotive and Armaments Command, and W. M. Keck Foundation. APS is supported by the DOE-BSE, Office of Energy Research, under contract W-31-109-Eng-38. The work performed at BL12XU, SPring-8, is partly supported by the National Synchrotron Radiation Research Center and National Science Center of Taiwan.

21 July 2006; accepted 14 September 2006
10.1126/science.1132884

Colloid Transport of Plutonium in the Far-Field of the Mayak Production Association, Russia

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Sorption of actinides, particularly plutonium, onto submicrometer-sized colloids increases their mobility, but these plutonium colloids are difficult to detect in the far-field. We identified actinides on colloids in the groundwater from the Mayak Production Association, Urals, Russia; at the source, the plutonium activity is ~1000 becquerels per liter. Plutonium activities are still 0.16 becquerels per liter at a distance of 3 kilometers, where 70 to 90 mole percent of the plutonium is sorbed onto colloids, confirming that colloids are responsible for the long-distance transport of plutonium. Nano–secondary ion mass spectrometry elemental maps reveal that amorphous iron oxide colloids adsorb Pu(IV) hydroxides or carbonates along with uranium carbonates.

Submicrometer-sized colloids, consisting of inorganic and/or organic compounds, occur at up to 10^{17} particles per liter in groundwater and provide an important means of transporting elements with low solubilities, including the actinides (*1*–*3*). The stability of these colloids is a function of the composition of groundwater and the hydrologic conditions (*4*).

The formation of actinide pseudo-colloids, in which the actinide sorbs onto aquatic colloids, can stabilize actinides in natural waters and increase their concentrations by many orders of magnitude over the values expected from solubility calculations (*2*, *5*). The association of Pu with colloids 25 to 450 nm in size has been observed 3.4 km from a source at Los Alamos National Laboratory (*6*). This migration distance is greater than modeled estimates (*7*). Similar transport has also been seen at the Savannah River Site (*8*). At Nevada Test Site, Pu has migrated 1.3 km in 30 years in groundwater by means of colloids with sizes of 7 nm to 1 μm (*9*). Model results imply that colloid-facilitated transport of actinides at Yucca Mountain could lead to as much as a 60-fold increase in the total effective dose equivalent to an exposed population (*10*).

Colloid-facilitated transport is likely the means for actinides' long-distance transport in groundwater. Many previous studies have experimentally demonstrated adsorption of Pu onto a variety of minerals and mineral assemblage (*11*–*13*). However, little is known of the speciation of the actinides or the type of colloids with which they are associated, particularly during the transport in the far-field where there are many competing processes, such as desorption from the colloids and resorption onto minerals.

To understand the colloid-associated actinides and their long-distance transport in groundwater, we investigated Pu migration in the natural groundwater system at one of the most contaminated nuclear sites in the world: Mayak, Russia. Mayak is a nuclear waste reprocessing plant near Kyshtym, in the Southern Urals, Russia (*14*) (Fig. 1). Waste effluents containing ^{90}Sr, ^{137}Cs, ^{241}Am, and ^{239}Pu were discharged into Lake Karachai (*15*, *16*); these were weakly alkaline $NaNO_3$ brine solutions with a pH of 7.9 to 9.3 and a salt concentration of 16 to 145 g/liter. The major dissolved ionic species were NO_3^- (11 to 78 g/liter), CH_3COO^- (0.6 to 20 g/liter), $C_2O_4^{2-}$ (0.9 to 14 g/liter), SO_4^{2-} (0.12 to 1.3 g/liter), Na^+ (6 to 32 g/liter), Cl^- (20 to 350 mg/liter), U(VI) (13 to 196 mg/liter), Ca^{2+} (8 to 80 mg/liter), and

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Mg^{2+} (8 to 69 mg/liter) (*17*). Lake Karachai is connected to the 55- to 100-m-thick groundwater zone, in which fluids flow through fractured Silurian and Devonian metavolcanic rocks with andesitic and basaltic composition (*17*). We completed systematic analyses of the composition and redox state of groundwaters and filtered samples, and we characterized the actinides associated with the colloids (*18*).

Because of the high concentration of NO_3^- in waste effluents, we used the presence of NO_3^- as a measure of the extent to which the contaminant plume had penetrated the groundwater system. The Pu radioactivity was ~4.8 becquerels (Bq)/liter at 0.05 km from the source, whereas it was ~0.029 Bq/liter at 4.0 km (Table 1), which is approximately equivalent to ~2.1 parts per trillion (ppt) and ~0.013 ppt, respectively, versus ~1000 Bq/liter (*19*) in the waste effluent. The redox potential, *Eh*, of the groundwater was +50 to ~+480 mV, and the pH was ~6 to 8. Nitrate concentrations decreased as distance from the source increased, although at greater depths (~100 m) original waste effluents with a relatively high concentration of Pu (0.16 Bq/liter) were present even 3.9 km from the source.

To understand stable chemical species of the actinides under the groundwater conditions, we constructed predominance diagrams for U and Pu species using thermodynamic calculation (*20*) with updated solubility data (*21*), based on the total concentrations of the groundwaters from the wells nearest to the source (Fig. 2, A and B) and from a well located 3.2 km away [well number 1, drilled in 1969 (1/69)] (Fig. 2, C and D). This analysis implies that $UO_2(CO_3)_2^{2-}$ is the dominant species near the source, whereas $UO_2(CO_3)_3^{4-}$ is present at well 1/69. However, the data (circles in Fig. 2, A and C) are close to the equilibrium boundary between these two U carbonate species. Thus, it is likely that both of these U(VI) carbonate species are dominant in the groundwater of Mayak, which is consistent with the oxidation state analysis (table S1). In addition, the U distribution on the colloidal matter for fractions of different sizes also indicates that 80 to 90% of the U is present as a soluble species (Fig. 2E). Similarly, most of the Np (70 to 80%) is present as a soluble Np(V) phase (Fig. 2E and table S1), most likely as NpO_2^+, as anticipated from the stability diagram (fig. S1).

The stability diagrams (Fig. 2, B and D) show that the total groundwater compositions near the source (solid square) and at the well 1/69 (open square) are in the region of solid PuO_2. Even though the solution is supersaturated with respect to crystalline plutonium dioxide $PuO_{2(c)}$, the precipitation will require aging in order to dehydrate the metastable Pu hydroxyl species into $PuO_{2(c)}$ (*21*, *22*). Given that amorphous $Pu(OH)_4$ always precipitates from solution instead of PuO_2 (*21*), the stability field of amorphous plutonium hydroxide $Pu(OH)_{4(am)}$ is also shown. The size dependence of the Pu distribution (Fig. 2E) shows that ~30 and ~10% of Pu is present as a soluble species in well 63/68 (near the source) and 1/69, respectively, which indicates that the actual Pu concentration in the "solution" was lower than the total Pu concentration in the groundwater. Because particles smaller than ~1 nm (the size of the 3-kD filter) were counted as a soluble species, a part of the Pu associated with the colloids, which are <1 nm, may have been counted as part of the soluble fraction. The

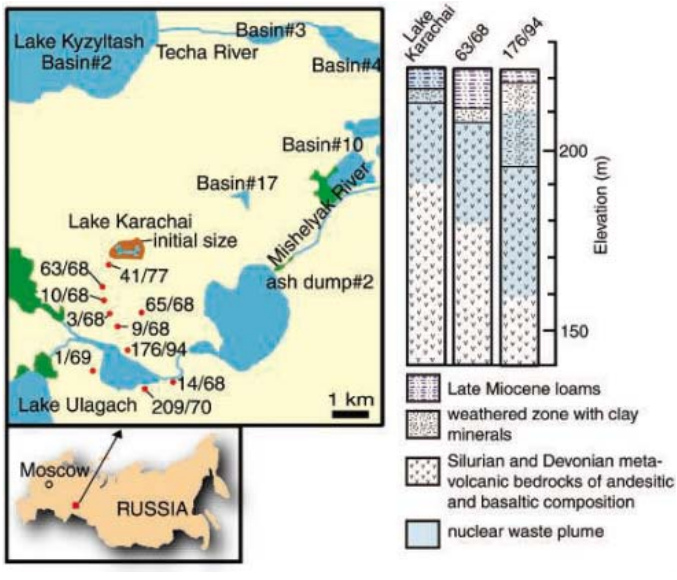

Fig. 1. Map of the study area. The locality map and stratigraphy are modifications of those in (*17*). The Mayak site covers ~160 km^2 (*17*). Red points labeled with the numbers are wells. The numbered basins are natural or man-made reservoirs for nuclear waste fluids.

Table 1. Concentration of actinides in the groundwaters from the Mayak region, Russia. The well index represents the well number followed by the drilling year (e.g., 41/77 is well 47, drilled in 1977). I.C., concentration of total inorganic carbon species in solution; n.d., not determined.

Well index	Distance (km)	Depth (m)	*Eh* (mV)	pH	I.C. (ppm)	NO_3^- (ppm)	$^{239,240}Pu$ (Bq/liter)	^{241}Am (Bq/liter)	^{237}Np (Bq/liter)	^{238}U (ppm)
Source	0.0					<78,000	1,000	420	41	25
41/77	0.05	20	+480	5.9	4,760	45,000	4.8	0.91	0.14	n.d.
		45	+50	8.05	n.d.	n.d.	2.8	0.34	0.12	n.d.
63/68	1.1	20	+400	6.0	1,220	45,000	0.13	0.21	18.2	20
		100	+60	7.33	n.d.	n.d.	0.31	1.32	11.1	38
10/68	1.5	60	+390	6.6	1,830	52,000	0.86	4.75	9.1	24
		100	+330	6.6	n.d.	n.d.	0.18	0.50	17.0	47
65/68	1.75	60	+300	7.5	n.d.	28,000	0.46	0.72	2.8	0.3
		100	+200	6.9	n.d.	n.d.	0.052	0.094	2.2	1.1
3/68	1.9	60	+350	7.1	1,160	32,000	1.62	0.29	10.4	38
		100	+300	6.45	n.d.	n.d.	1.19	0.40	12.2	43
9/68	2.15	60	+310	7.60	952	27,100	0.036	1.10	5.8	26
		100	+350	5.85	n.d.	n.d.	0.21	1.08	10.9	36
176/94	2.5	27	n.d.	n.d.	n.d.	n.d.	3.0	0.7	0.36	3.2
		63	+90	7.33	251	3,910	0.8	0.11	0.78	2.8
1/69	3.2	44	+100	7.9	159	21	0.089	0.15	2.1	0.26
14/68	3.9	100	+100	7.9	200	498	0.16	0.087	2.5	19
209/70	4.0	40	+50	8.12	136	6.5	0.029	0.08	0.03	0.02

actual Pu concentration in the groundwater could have been even lower than the percentage shown in Fig. 2E. Thus, the data points for the actual soluble Pu concentrations should be plotted at lower values in the diagram of Fig. 2, B and D, as indicated by the arrows. In the event that an intrinsic Pu(IV) phase precipitates from solution, the Pu concentrations in solution (data points in Fig. 2, B and D) will also be shifted downward to the stability field of aqueous plutonium hydroxide $Pu(OH)_{4(aq)}$ (the dashed arrows).

A dominant fraction of $Pu(OH)_{4(aq)}$ is not inconsistent with the oxidation state analysis that reveals a predominance of Pu(IV), although it is also possible that different chemical Pu(IV) species are incorporated into aquatic colloids. In addition, 70 to 90% of Pu was associated with the colloidal fraction on 3- and 10-kD filters (the size range of 1 to 15 nm). The ratio of Pu associated with colloids to soluble species (Fig. 2F) was nearly constant (~2.2) within 2.15 km of the source, regardless of the Pu concentration, and the values became higher (>5) at distances of >2.5 km (Fig. 2F) as well as U partitioning (Fig. 2G). This result suggests that Pu was partitioned between colloids and soluble species within 2.5 km, whereas at >2.5 km, the excess fraction of Pu-bearing colloids is transported in the groundwater system, ascribed to a disequilibrium derived from the slow desorption of Pu from the colloids or to the irreversible incorporation of trace Pu into aquatic colloids.

Electron microscopy analysis of the colloid fraction from well 1/69 revealed a variety of phases (Fig. 3A). Spherical Fe oxide and Fe hydroxide are the most abundant phases, and they are associated with minor Si and Ca that range in size from a few nanometers to 100 nm across, forming aggregates up to several micrometers in size (Fig. 3, B and C). Based on the electron diffraction pattern, the Fe oxide/hydroxide is characterized to be an amorphous Fe hydroxide (HFO). Amorphous HFO commonly occurs in soils and is known to be an efficient adsorbent of toxic metals (*23*). The other identified phases include clays and calcite; rutile, hematite, barite, and rancieite; and monazite, in decreasing order of abundance. Nano–secondary ion mass spectrometry (SIMS) elemental maps for the colloids from well 1/69 reveal that some Al and Mn are also associated with the Fe (Fig. 3D). The approximate atomic ratios of Al to Fe and Mn to Fe are ~0.003 and ~0.004, respectively. The amount of associated Ca is not less than the amount of Al and Mn but is at the same level as in the mixture of HFO (Fig. 3C). Thus, this aggregate of colloids can be characterized as amorphous HFO adsorbing less than 1 atomic % of Al and Mn.

The Pu map (Fig. 3D) is nearly the same as that of the U, which is associated with the Fe oxide. Semiquantitatively, the atomic ratio of U to Fe is ~0.0004, and the ratio of Pu to U is ~0.03, indicating that amorphous HFO is a pseudo-colloid sorbing both the Pu and U. Based on the thermodynamic calculations for the expected, dominant Pu and U species, $Pu(OH)_{4(aq)}$ occurs with $UO_2(CO_3)_3^{4-}$ and to a lesser extent with $UO_2(CO_3)_2^{2-}$, subsequently sorbing onto the amorphous HFO. Because the SIMS analysis causes the destruction of the sample, there are no crystallographic data available for the same HFO grain for which Pu was detected by nano-SIMS and examined by electron microscopy. Elemental mapping of the other colloidal material showed that U is predominantly adsorbed onto amorphous HFO and to a lesser extent onto rancieite $[(Ca,Mn)Mn_4O_9 3H_2O]$ and hematite (Fe_2O_3) (fig. S2). We did not find any intrinsic Pu(IV) colloids nor any actinide adsorption onto the other colloidal phases, including clays, calcite, rutile, barite, and monazite in the sample from well 1/69. These results are consistent with experiments that have reported a higher adsorption coefficient for Pu onto Fe oxide colloids than onto montmorillonite and silica (*24*). Additionally, the high ionic strength of this system may inhibit adsorption onto inorganic colloids, with the exception of Fe oxide (*24*). At distances greater than 2.5 km, the desorption process is anticipated to occur slowly, because the previous experiments revealed that the Pu desorption process from a hematite surface is considerably slower than the adsorption rate (*24*). Based on the Pu adsorption onto amorphous HFO in this system, most Pu(IV) in our oxidation analysis (table S1) may be the result of reduction of Pu(V) to Pu(IV) after adsorption

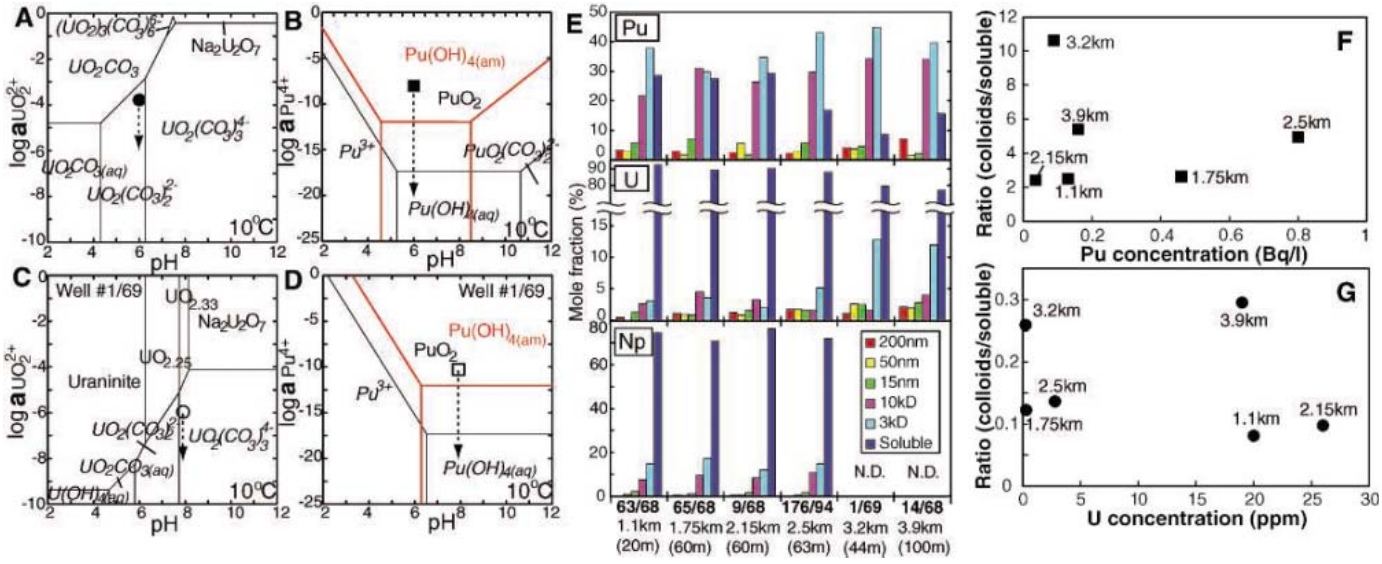

Fig. 2. Stable species of actinides and evidence of actinides bound to colloids. (**A** and **B**) Thermodynamic stability diagrams of U and Pu species under the conditions near Karachai Lake (well 41/77). (**C** and **D**) Thermodynamic stability diagram of U and Pu species under the conditions at well 1/69 located 3.9 km from the source at a depth of 44 m. Total concentrations in the groundwater are plotted as circles (U) and squares (Pu). Solid symbols show data near the source [(A) and (B)], and open symbols show the data at well 1/69 [(C) and (D)]. Roman and italic fonts represent solid and aqueous species, respectively. The arrows indicate the transition of solution composition that occurs when Pu precipitates as intrinsic or aquatic colloids or is sorbed onto pseudo-colloids. For these thermodynamic calculations, Act-2 application (*20*) was used with the database of thermo.com.v8.r6+, which is an expanded version of the Lawrence Livermore National Laboratory database. Solubility data of $Pu(OH)_{4(aq)}$ are updated based on (*21*). In illustrating the stability fields (red) of $Pu(OH)_{4(am)}$ in (B) and (D), the temperature was set to 25°C because of the limited solubility data in (*21*). (**E**) Mole fraction of actinides (Pu, U, and Np) bound to colloids as a function of the size. The 10- and 3-kD measures correspond to approximately 1.5 and 1.0 nm, respectively. N.D., not determined. (**F** and **G**) Ratios between actinides bound to colloids and in a soluble form for Pu and U. Pu and U concentrations are a total in the groundwaters. ppm, parts per million.

onto Fe oxide (*11*, *12*). In addition, the high concentration of dissolved organic carbon (<20 g/liter of CH_3COO^-) near the source may result in the reduction of Pu(V) into Pu(IV) in solution, as reported in (*12*, *22*). Even inorganic colloids can be coated by humic acid, forming pseudocolloids, which can sorb the hydrolyzed species more strongly than simple inorganic colloids (*22*).

As compared with other minerals that may sorb actinides, the Fe oxides have a high zero point of charge (ZPC): 6.5 for Fe_3O_4 and 7.8 for α-FeOOH versus 4.6 for kaolinite, 2.5 for montmorillonite, 2 to 2.4 for feldspars, and 2.0 for SiO_2 (*25*). In particular, the ZPC for amorphous $Fe(OH)_3$ is 8.5 (*25*), and the value should be the most appropriate for the HFO we found because of the amorphous structure of the Fe oxide/hydroxide. The high ZPC must result in the positive charge on the surface of HFO under the conditions in the Mayak groundwaters; thus, the particles should be efficient adsorbents of negatively charged U species. Although it is not evident how $Pu(OH)_{4(aq)}$ is adsorbed onto the HFO together with $UO_2(CO_3)_3^{4-}$, the hydroxyls of $Pu(OH)_{4(aq)}$ may be attached directly to the positively charged HFO surface. According to recent modeling studies (*26*), a Pu(IV) carbonate species, $Pu(CO_3)_3^{2-}$, is also possible at pH > 7 in equilibrium with the atmosphere. Another study (*27*) has also suggested that Pu carbonate species could also be dominant at Mayak (fig. S3), although the latest compilation of the thermodynamic database for Pu speciation gives only the maximum possible value for the equilibrium constant of this species because the experimental data are scattered (*28*). Thus, the carbonate species was not included in the calculations used to produce Fig. 2, B and D. If the Pu is present as a carbonate species in the Mayak system, the negatively charged Pu species can be sorbed by HFO, as could the U carbonate species. Ultimately, the polymerization of carbonate species might result in Pu association with U. Although further analysis is required, we conclude that both Pu and U species are adsorbed similarly onto the HFO surface.

The subsurface migration of Pu from Lake Karachai over more than 4 km within ~55 years after discharge is comparable to the transport rate seen at the Nevada Test Site (1.3 km/30 years minimum) (*9*). Up until now, there has been an argument over which colloidal phase carries Pu and how they associate. Our evidence of Pu sorption onto the specific colloidal phase is applicable to systems that are dominated by U under oxidizing conditions, such as the proposed repository at Yucca Mountain in Nevada. Because of differences in physicochemical conditions, site-specific investigations of actinide colloids in the far-field are necessary at each potential nuclear waste repository site.

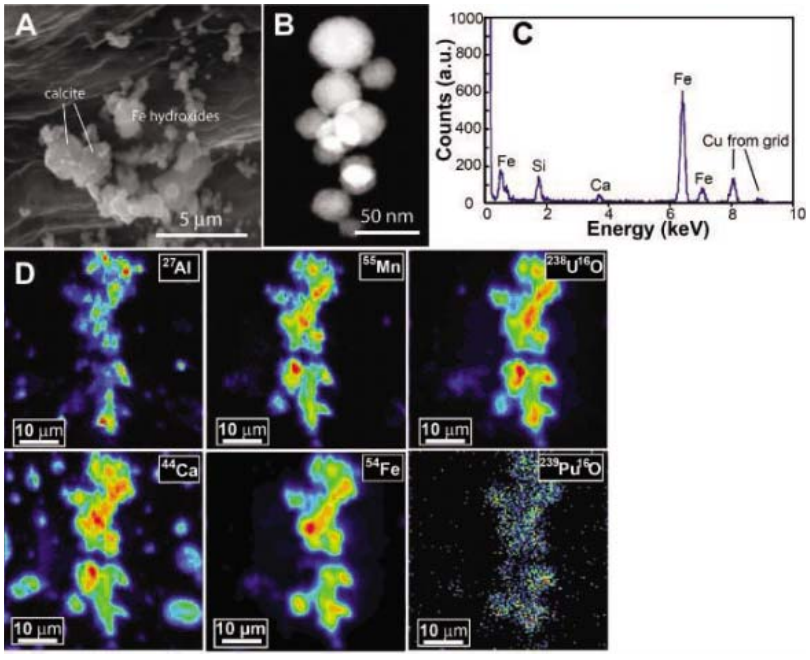

Fig. 3. Direct evidence of Pu adsorption onto amorphous Fe hydroxide. (**A**) Scanning electron micrograph of typical colloids from well 1/69. Many spherical particles were observed with a size of <1 μm. (**B**) High-angle annular dark-field scanning transmission electron microscopy image of the spherical colloids. Electron diffraction patterns from these particles indicate that they are amorphous. (**C**) Energy dispersive x-ray spectrum from the spherical particles shows that Fe is a major constituent associated with trace amounts of Si and Ca. a.u., arbitrary units. (**D**) Nano-SIMS elemental maps. Because the contrast of these maps has been enhanced to show the distribution clearly, the intensity of the color in the chemical maps corresponds to the relative concentration for each element but cannot be used to compare one element to another.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5799/638/DC1
Materials and Methods
Figs. S1 to S3
Table S1
References

15 June 2006; accepted 8 September 2006
10.1126/science.1131307

Thrice Out of Africa: Ancient and Recent Expansions of the Honey Bee, *Apis mellifera*

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We characterized *Apis mellifera* in both native and introduced ranges using 1136 single-nucleotide polymorphisms genotyped in 341 individuals. Our results indicate that *A. mellifera* originated in Africa and expanded into Eurasia at least twice, resulting in populations in eastern and western Europe that are geographically close but genetically distant. A third expansion in the New World has involved the near-replacement of previously introduced "European" honey bees by descendants of more recently introduced *A. m. scutellata* ("African" or "killer" bees). Our analyses of spatial transects and temporal series in the New World revealed differential replacement of alleles derived from eastern versus western Europe, with admixture evident in all individuals.

The long-standing association between humans and honey bees, *Apis mellifera*, is evidenced by 7000-year-old cave paintings depicting honey collection from wild bee nests (*1*). Managed honey bee colonies satisfy the pollination requirements of both modern agriculture and the demand for products such as honey, wax, and royal jelly (*2*). With the publication of the honey bee genome sequence (*3*) and development of high-density single-nucleotide polymorphism (SNP) markers, tools are now available to study evolutionary processes occurring in both native and introduced populations, including Africanization in the New World, and the genomewide consequences of ancient and recent evolution in this important social insect.

The genus *Apis* comprises 10 species, 9 of which are confined to Asia (*4*). *A. mellifera*, however, is distributed from sub-Saharan Africa to central Asia and northern Europe and is composed of more than two dozen morphologically and geographically distinct subspecies (*5*). It is commonly believed that *A. mellifera* split from its closest relative, *A. cerana*, in western or central Asia (where these species' ranges are closest) and subsequently expanded into Europe and Africa (*5*, *6*). Existing populations in Europe and Africa are hypothesized to derive from populations currently found in Asia, where *A. mellifera* occurs as far east as Kazakhstan (*6*). However, an apparent discrepancy between the age of divergence among *A. mellifera* subspecies [0.7 to 1.3 million years (*4*, *5*, *7*)] and the split 6 to 8 million years ago (*4*, *7*, *8*) between *A. mellifera* and *A. cerana* suggests alternative scenarios. One hypothesis [suggested by E. O. Wilson, citing a personal correspondence from C. D. Michener (*9*)] is that *A. mellifera* originated in the tropics or subtropics of Africa.

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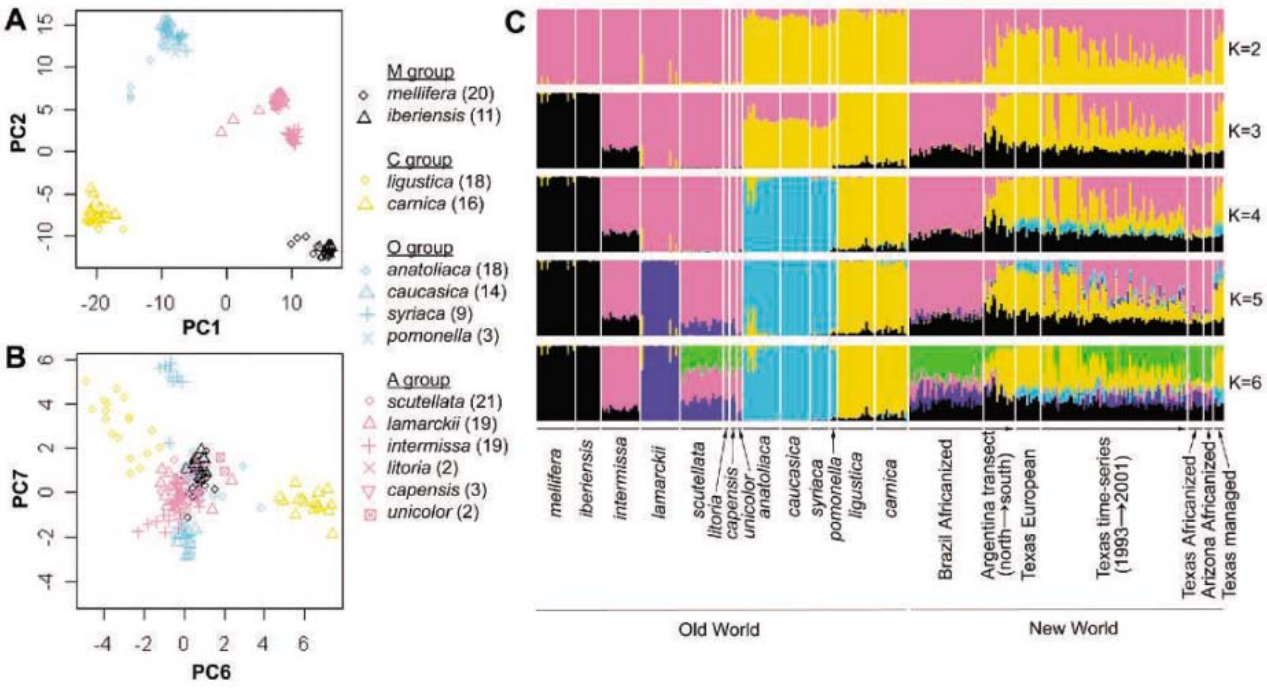

Fig. 1. Patterns of genetic variation in *A. mellifera*. (**A** and **B**) Principal component plots of Old World individuals based on the 1136 SNP loci (*22*). (A) Bees cluster in four main groupings (M, C, O, and A) in the coordinates of PC1 and PC2. (B) Higher order PCs partition geographical subspecies. See figs. S1 and S2 for additional PCA results. (**C**) Results of *Structure* analysis (*22*). Individuals are represented by vertical lines, grouped by geographical subspecies (Old World) or sampling regime (New World). Division of individuals into colored segments represents the probability of assignment of that individual to each of *K* groups. *K* represents an arbitrary number of hypothetical populations, shown on the right. Colors for *K* = 4 correspond to colors used in PCA (A and B) and Fig. 2, A and C to I.

In North America, introductions of the subspecies *Apis mellifera mellifera* began as early as 1622. Subsequent introductions of *A. m. ligustica* (the "Italian" bee) began in 1859, followed by introductions of at least seven other subspecies from Europe, the Near East, and northern Africa (the descendants of which are collectively called "European") (*10*). Early introductions in South America are less clear, but probably also involved

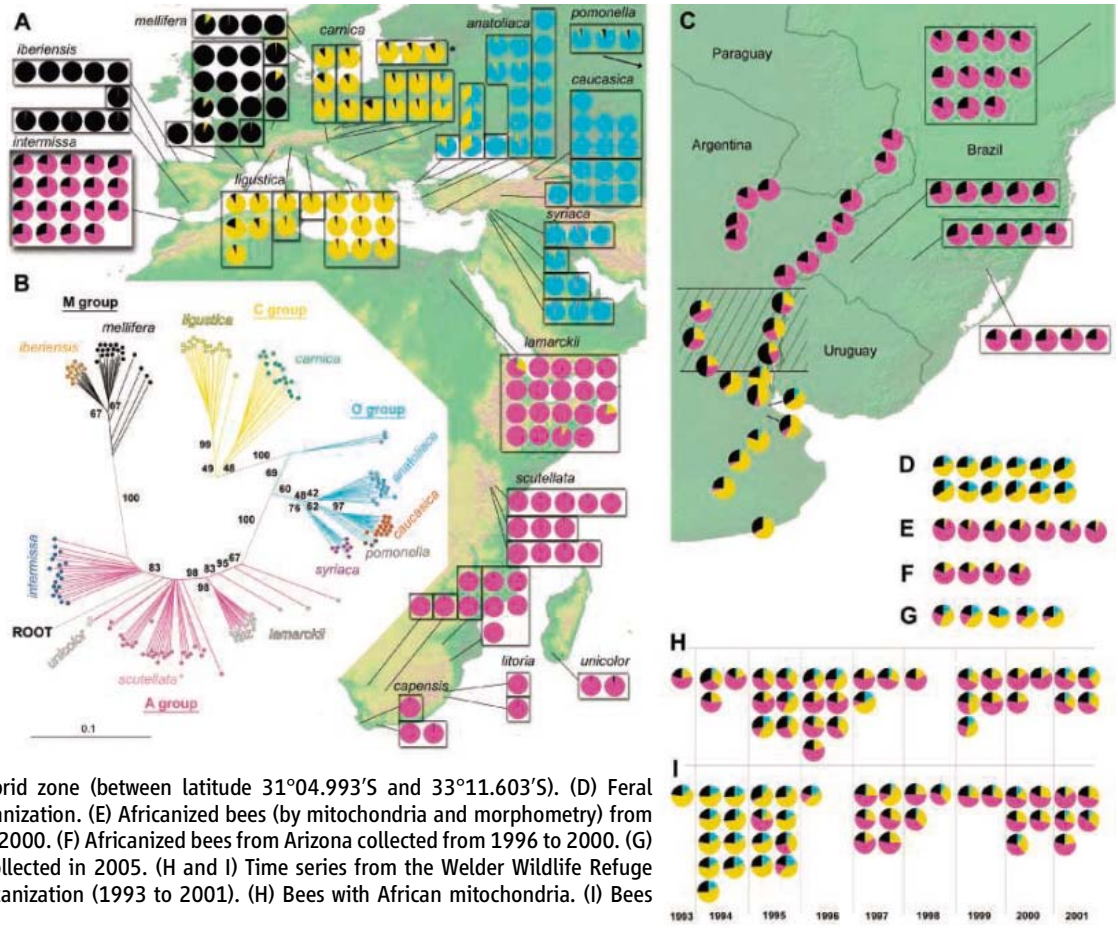

Fig. 2. Geographical and temporal patterns of diversification. (**A**) Assignment probabilities from *Structure* analysis (Fig. 1C, $K = 4$) of Old World individuals. *A. m. pomonella* ($N = 3$) collected from Kyrgyzstan. Three *A. m. carnica* (indicated by asterisk) were provided by a research facility. (**B**) Neighbor-joining tree based on allele-sharing distance. "ROOT" represents a single derived genotype consisting of 289 SNPs with one common homozygous genotype from *A. cerana* ($N = 7$) and *A. dorsata* ($N = 4$) (*32*). Branches are colored to correspond to the four groups in (A). The group labeled *scutellata** also includes *A. m. litoria* ($N = 2$) and *A. m. capensis* ($N = 3$). (**C** to **I**) *Structure* analysis (Fig. 1C, $K = 4$) of New World individuals. (C) Geographic distribution of Africanization in South America. Hatched region denotes hybrid zone (between latitude 31°04.993′S and 33°11.603′S). (D) Feral bees from Texas before Africanization. (E) Africanized bees (by mitochondria and morphometry) from Texas collected from 1996 to 2000. (F) Africanized bees from Arizona collected from 1996 to 2000. (G) Managed bees from Texas collected in 2005. (H and I) Time series from the Welder Wildlife Refuge (southern Texas) during Africanization (1993 to 2001). (H) Bees with African mitochondria. (I) Bees with European mitochondria.

Table 1. Candidate loci for selection. Subset of outlier SNPs from Fig. 3A (Set 1) and Fig. 3B (Set 2) (see table S3). The frequency of predominant *A. m. scutellata* allele is indicated. Syn, synonymous codon change. Groups for South and North America are as indicated in Fig. 2 (arranged by increasing Africanization from left to right). UTR, untranslated region; UV, ultraviolet; GTPase, guanosine triphosphatase; PKG, cGMP-dependent protein kinase.

	Old World				South America			North America							
SNP	*ligustica*	*mellifera*	*scutellata*	*caucasica*	South	Hybrid zone	North	European	1993–1995	1996–1998	1999–2001	Africanized	Near or affected gene	SNP position or effect	Gene product
								Set 1							
est6550	0.00	0.95	1.00	1.00	0.06	0.83	0.99	0.21	0.38	0.64	0.88	0.91	GB11704	5′ UTR	
ahb7495	0.00	0.94	0.97	0.00	0.13	0.42	0.97	0.08	0.29	0.50	0.46	0.91	GB10583 (*nAchRα3*)	†	Nicotinic acetylcholine receptor, α3 subunit
est8764	0.00	1.00	0.97	1.00	0.25	0.75	1.00	0.13	0.59	0.69	0.73	0.86	GB10830	S→A	
est9209*	0.03	0.98	1.00	0.36	0.19	0.75	0.97	0.21	0.54	0.62	0.79	0.91	GB10514(*Tubα1*)	Syn	Tubulin, α1 chain
est9211*	0.03	0.98	0.97	0.32	0.19	0.75	0.97	0.21	0.55	0.67	0.79	0.95	GB10514 (*Tubα1*)	Syn	Tubulin, α1 chain
								Set 2							
ahb12140	0.00	0.00	1.00	0.00	0.00	0.33	0.76	0.04	0.20	0.38	0.44	0.73	GB18171 (*UVop*)	Syn	UV-sensitive opsin
ahb11258	0.00	0.00	0.92	0.00	0.00	0.25	0.74	0.00	0.21	0.40	0.65	0.86	GB15150	Intron	GTPase activator
ahb11774	0.08	0.03	0.94	0.00	0.00	0.50	0.76	0.04	0.23	0.55	0.54	0.50	GB15050	~1500 bp 5′	
est424	0.25	0.20	0.97	0.00	0.19	0.92	0.92	0.17	0.41	0.45	0.71	0.86	GB19539	Syn	
est10185	0.00	0.00	0.91	1.00	0.06	0.50	0.81	0.13	0.32	0.57	0.58	0.45	GB18394 (*for*)	3′ UTR	*foraging*; PKG
ahb9731	0.00	0.05	0.78	0.00	0.00	0.17	0.69	0.00	0.18	0.57	0.50	0.77	GB15214	Syn	

*These two SNPs are 939 base pairs (bp) apart. †Approximately 3000 bp 5′ of start codon for gene prediction GB10583; this gene has an alternate predicted structure (S.C_Group5.24000030B) (*3*) that places the SNP 30 bp upstream of the start codon.

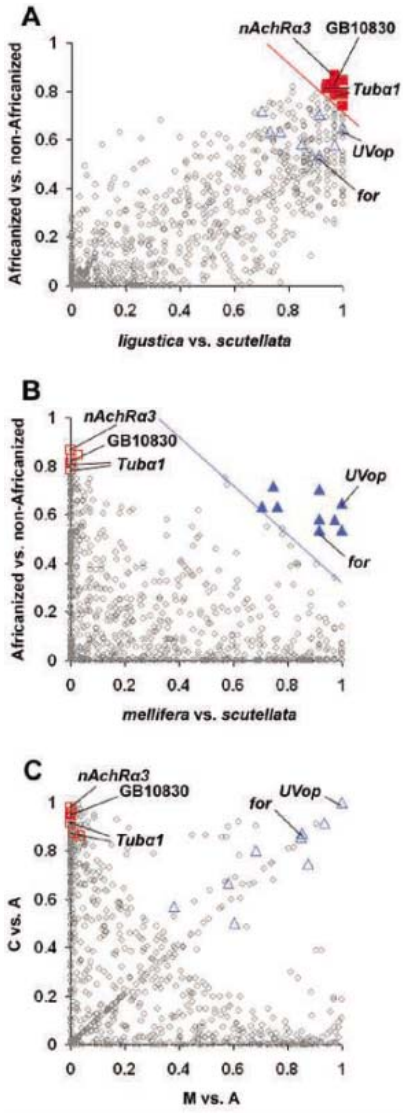

Fig. 3. F_{ST} of 1136 SNPs in introduced and native populations. (**A**) Differentiation in the New World (Africanized versus non-Africanized; *y* axis) largely corresponds to differentiation between *A. m. scutellata* and *A. m. ligustica* (*x* axis). Filled red squares represent the 1% of SNPs exhibiting the highest differentiation in both axes (Table 1 and table S3, "Set 1"). (**B**) SNPs exhibiting high differentiation between *A. m. scutellata* and *A. m. mellifera* (*x* axis) exhibited little differentiation in the New World (*y* axis). Filled blue triangles represent the 1% of SNPs exhibiting the highest differentiation in both axes (Table 1 and table S3, "Set 2"). (**C**) Few SNPs exhibit high differentiation in both C and M lineages relative to A, consistent with independent derivation of eastern and western European subspecies from Africa. Set 2 loci generally exhibit high differentiation in the New World (B, filled blue triangles) and in the two Old World lineages independently derived from Africa (C, open blue triangles). Several SNPs occurring in or near genes are indicated (abbreviations as in Table 1). "Africanized" refers to all individuals in Fig. 2, C (north of hybrid zone), E, and F. "Non-Africanized" refers to all individuals in Fig. 2, C (south of hybrid zone) and D.

early introduction of western European subspecies (*A. m. mellifera* and *A. m. iberiensis*) and later introduction of eastern European subspecies (*10*). In 1956, a subspecies from the African savannas, *A. m. scutellata*, was intentionally introduced to Brazil. *A. m. scutellata* became established and dispersed northward and southward from Brazil through South and Central America (*11*–*13*), hybridizing with and displacing previously introduced honey bees. Africanized bees reached their southern limit in Argentina in the 1970s (*14*), but the eventual northward limit in the United States [first invaded in 1990 (*15*)] is unknown. Although ample evidence shows that both European and African alleles occur in Africanized populations (*14*, *16*–*21*), *A. m. scutellata*–derived characteristics, including nesting biology, swarming and absconding behavior, foraging, diet, and mitochondrial DNA (mtDNA), tend to displace European characteristics over time (*13*).

We analyzed 1136 SNP genotypes (*22*, *23*) from 328 *A. mellifera*, including 175 individuals from native populations (representing 14 subspecies in Europe, Africa, and Asia) and 153 individuals from introduced populations in North and South America. We inferred the ancestral genotype for a subset of SNPs by analyzing 13 additional individuals from 3 congeneric species, *A. cerana*, *A. dorsata*, and *A. florea*.

In the Old World, there was clear population structure at the level of major groups (each containing multiple subspecies) and geographical subspecies. Principal component analysis (PCA) revealed four major clusters (Fig. 1A) consistent with Ruttner's four morphometrically defined lineages (*5*, *24*): M (western and northern Europe), C (eastern Europe), O (Near East and central Asia), and A (Africa). The four groups were broadly consistent with mitochondrial data (*25*) and with assignment by the program *Structure* (Fig. 1C) (*22*). Pairwise F_{ST} between major groups ranged from 0.242 to 0.565 (table S2).

Each of the 10 geographical subspecies with 9 to 20 individuals was genetically distinct, and subspecies could be partitioned in either PCA or *Structure* analysis (Fig. 1B; figs. S2 and S3). F_{ST} among subspecies was 0.501; much lower values were obtained for subspecies within each of the major groups (0.053, 0.129, 0.118, and 0.082 for M, A, O, and C, respectively). Despite considerable differentiation, admixture between geographically proximal populations in the Old World was evident in both PCA (Fig. 1A) and *Structure* analysis (Figs. 1C and 2A). Comparison of linkage disequilibrium (LD) between subspecies (fig. S4) also suggested differences related to admixture, bottlenecks, or both. For example, *A. m. mellifera* and *A. m. ligustica* exhibited relatively high LD for SNP pairs separated by ≤10 kb (mean correlation coefficient r^2 of 0.45 and 0.30, respectively, decreasing to 0.18 and 0.06 for SNP pairs separated by 50 to 100 kb). In contrast, *A. m. scutellata* and *A. m. intermissa* exhibited relatively little or no LD (0.08 and 0.13 for ≤ 10 kb; 0.07 and 0.10 for 50 to 100 kb). LD was low overall and affected only a small number of SNPs (fig. S4), consistent with extraordinarily high recombination rates in *A. mellifera* [~19 cM/Mb (*26*)].

To explore evolutionary relationships, we generated distance trees using Old World *A. mellifera*, and rooted these trees using an ancestral genotype derived from *A. cerana* and *A. dorsata*. The two groups that comprise European bees (M and C) were the most distantly related, despite their geographic proximity, and M was considerably more similar to A (F_{ST} = 0.242) than to either C or O (F_{ST} = 0.565 and 0.458, respectively) (Fig. 2B, table S2). Unexpectedly, the tree was rooted in Africa (Fig. 2B). Tree rooting and other relationships had strong bootstrap support and were essentially the same when we used parsimony-based methods, alternative SNP subsets, or genotypes from congeneric individuals (rather than a single derived ancestral genotype) (figs. S5 to S7). On the basis of these data, we hypothesize that *A. mellifera* originated in Africa and that there were at least two subsequent expansions into Eurasia—a western expansion into Europe (M) and one or more (independent) eastern expansions into Asia and Europe (O and C).

New World bees collected in Brazil (the original site of *A. m. scutellata* introduction in 1956) were highly Africanized, although all individuals exhibited introgression with the M group (Figs. 1C and 2C; fig. S1). Similar levels of introgression were not evident in any *A. m. scutellata* from Africa (Figs. 1C and 2A; fig. S1.) Two parallel transects in northern Argentina revealed transitions from predominantly African genotypes (north) to predominantly C group genotypes (south) (Fig. 2C and fig. S1B; table S2). *Structure* analysis revealed a consistent minority of M group alleles (Fig. 2C, black) in all individuals north and south of the hybrid zone. Retention of several M group markers has been observed at the population level (*13*); our results indicate that this effect occurs at the individual level. The location of the hybrid zone (Fig. 2C) appears to be stable, matching the general latitude of transition from Africanized to European bees in previous studies published in 1982 and 1991 (*14*, *27*).

Feral bees collected in the United States before Africanization were of mixed Eurasian ancestry, dominated by C group but admixed with M and O groups (Fig. 2D and fig. S1A). After Africanization, bees defined as Africanized by morphology exhibited predominantly African ancestry admixed with M, C, and to a lesser extent, O group bees (Fig. 2, E and F; fig. S1A). During Africanization, bees from southern Texas (1993 to 2001) showed a transition from mixed European to substantially, but not exclusively, African ancestry (Fig. 2, H and I; fig. S1C). Individuals in early (1993 to 1995), middle (1996 to 1998), and late collections (1999 to 2001) with African mtDNA were predominantly African at nuclear loci (Fig. 2H, table S2). In contrast, bees with European mtDNA became progressively differentiated from *A. m. ligustica* (C group) and increasingly similar to *A. m. scutellata* (Fig. 2I, table S2). In North America, as in South America,

an unexpectedly consistent minority of M group alleles was evident in all genomes of both non-Africanized and Africanized individuals (Fig. 2, D to I, black). Recently collected bees (1999 to 2001) with African and European mtDNA were virtually indistinguishable at the SNP loci (Fig. 2, H versus I; table S2).

To identify loci with extreme patterns of differentiation, possibly due to natural selection (*28*), we calculated F_{ST} among Old and New World bees at all 1136 SNP loci (Fig. 3). Pairwise differentiation between non-Africanized and Africanized bees in the New World was highly correlated with differentiation between *A. m. ligustica* and *A. m. scutellata* in the Old World (Fig. 3A) (r = 0.81), consistent with the hypothesis that Africanization involves replacement of *A. m. ligustica* alleles by *A. m. scutellata* alleles (SNPs with the highest levels of differentiation in both comparisons are indicated in Fig. 3A by filled red squares and in Table 1 and table S3 as "Set 1"). In contrast, most loci highly differentiated between *A. m. scutellata* and *A. m. mellifera* showed little differentiation between Africanized and non-Africanized bees (Fig. 3B) (r = −0.37), indicating that biased replacement of C- but not M-derived alleles [(*13*) and the present study] may occur throughout the genome. However, a small subset of loci that distinguish *A. m. mellifera* from *A. m. scutellata* also exhibited relatively high differentiation for Africanized versus non-Africanized New World bees (Fig. 3B, filled blue triangles). These few SNPs distinguished both C and M groups from the A group (Fig. 3C and Table 1).

Of 19 SNPs identified as potential sites for selection (Fig. 3), 11 occurred in or near genes (Table 1 and table S3). Six occurred in coding regions, but only one was predicted to cause a nonsynonymous amino acid change (in a gene of unknown function; Table 1). Although some of these SNPs may alter gene function, it is also possible that some or all have hitchhiked with linked polymorphisms that are under selection.

These data provide a global view of the population genetic structure of *A. mellifera*. Future studies can capitalize on the large number of SNPs presented here to further investigate population genetic patterns within and among populations and genes under selection.

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33. We thank K. Hartfelder, W. Rubink, C. Tillberg, C. Smith, S. Wittman, M. Sen Sarma, O. Kaftanoglu, O. R. Taylor Jr., R. Crewe, S. Goodman, and M. Sasaki for bee collections; K. Heeres for DNA extraction; S. Edelheit for SNP genotyping; A. Pinto for mitotyping; J. Pinter for genotype analyses and base calling; J. Theirrian for project coordination; and G. E. Robinson, B. S. Gaut, A. D. Long, and P. L. Morrell for advice and manuscript review. We thank M. Adams for facilities and personnel for SNP genotyping; and the Human Genome Sequencing Center, Baylor College of Medicine, and RIKEN for providing sequence data ahead of publication. This work was supported by the Institute for Genomic Biology, School of Integrative Biology, and the Research Board at the University of Illinois (C.W.W.), NSF (A.V.S.), U.S. Department of Agriculture and California Department of Consumer Affairs, Structural Pest Board (N.D.T.).

Supporting Online Material

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20 July 2006; accepted 5 October 2006
10.1126/science.1132772

Functional CpG Methylation System in a Social Insect

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DNA methylation systems are well characterized in vertebrates, but methylation in *Drosophila melanogaster* and other invertebrates remains controversial. Using the recently sequenced honey bee genome, we present a bioinformatic, molecular, and biochemical characterization of a functional DNA methylation system in an insect. We report on catalytically active orthologs of the vertebrate DNA methyltransferases Dnmt1 and Dnmt3a and b, two isoforms that contain a methyl-DNA binding domain, genomic 5-methyl-deoxycytosine, and CpG-methylated genes. The honey bee provides an opportunity to study the roles of methylation in social contexts.

Among the many important functions of CpG DNA methylation, sex-specific regulation of gene expression (imprinting) in vertebrates stands out because it provides insight into intragenomic conflict (*1*, *2*). Provided social insects have CpG methylation, they would be ideal models to further explore the kin-conflict theory of imprinting, because insect societies are composed of many different types of relatives and they interact with each other in many evolutionarily important contexts (*2*, *3*).

However, although widely conserved from yeast and fungi to plants to vertebrates, DNA methylation in insects is enigmatic. Evidence of CpG-methylated sequences exists for several insect species (*4*–*6*), but no bona fide invertebrate deoxycytosine methyltransferases (DNMTs) have been described. Conversely, the model insect *Drosophila melanogaster* shows limited DNA methylation, predominantly in asymmetric CpT and CpA dinucleotides (*7*), and this is attributed to the only DNMT family member encoded in its genome, dDNMT2, a $tRNA^{Asp}$ methyltransferase

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(*8*, *9*). The *Drosophila* situation renders the fragmentary findings from the other insect species uninterpretable.

Here, we report that a social insect, the honey bee, *Apis mellifera*, has a fully functional CpG methylation system. We present biochemical, molecular, and genomic analyses, made possible by the recently sequenced honey bee genome (*10*).

In addition to *Dnmt2*, we identified one ortholog for de novo methylation (*AmDnmt3*) and two orthologs for maintenance methylation (*AmDnmt1a* and *AmDnmt1b*) (Fig. 1A and fig. S1A). *AmDnmt1a* and *AmDnmt1b* encode 70% identical ~1400–amino acid proteins, which have 55% identity and 70% similarity to human DNMT1 over almost their entire length. Likewise, *AmDNMT3* shows strong sequence similarity to *hDNMT3A* and *hDNMT3B*, with 33 and 32% similarity over the whole gene and 61 and 66% identity in the catalytic domains, respectively.

The predicted AmDNMT-encoding genes are expressed in tissue-specific and developmentally regulated patterns (Fig. 1A). Protein extracts from bees (Fig. 1B) demonstrate the presence of catalytically active DNMT enzymes. In vitro biochemical analyses of the recombinant AmDNMT proteins confirmed that AmDNMT1A and AmDNMT3 are catalytically active DNMTs (Fig. 1C) with similar characteristics to their vertebrate orthologs (*9*).

The honey bee CpG methylation system is functional in vivo. We isolated 5-methyl deoxycytosine (dC^M) (*11*) from bee genomic DNA (Fig. 1D) and using the methods of (*12*) have so far identified six genes methylated in vivo (figs. S2 to S7). These analyses also revealed that non-CpG methylation is either extremely rare or nonexistent in honey bee. In each instance, the methylation was found exclusively in transcribed regions and predominantly in predicted exons with low G+C content and few CpGs overall. One methylated gene (*GB16767*) encodes an ortholog of mSin3A-associated protein 130 kD (SAP-130); Sin3 complexes regulate gene expression from yeast through humans (*13*), providing the potential for potent downstream genome-wide effects in honey bees.

Further analysis of the honey bee genome identified a gene homologous to the family of methyl-DNA binding domain (MBD) proteins (fig. S1B), some of which are effectors of DNA methylation (*14*). At least two expressed splicing variants exist, both of which contain the most highly conserved amino acids in the MBD (fig. S1B). AmMBD-l preferentially, but not exclusively, interacted with a methylated DNA probe in vitro (fig. S8, B and C), similar to MBDs in other species (*14*, *15*). The protein sequence, size, and in vitro binding characteristics indicate that AmMBD-l is most similar to the vertebrate MBD3 subfamily. MBD3 proteins across species vary in their methyl-DNA binding specificities in vitro (*14*) and function in vivo as integral components of the Mi-2 chromatin-remodeling complexes in both vertebrates and *Drosophila* (*15*, *16*). Alternatively, the translation of DNA methylation marks in the honey bee may be achieved through other mechanisms (*17*).

On the basis of our findings, it is now possible to reflect on the earlier insect work (*4*–*6*) and predict that vertebrate-like systems of methylation are widespread in insects. If so, then *Drosophila* is of interest, not as a general model of insect methylation, but for unexplored evolutionary aspects of genome regulation, including the lack of a canonical telomeric (TTAGG) repeat (*18*), the pairing of homologous chromosomes throughout interphase (*19*), and the lack of symmetrical or CpG methylation (*7*).

Our findings also mean that the honey bee has the mechanisms that underlie imprinting, so tests of the kin-conflict theory in social insects are likely to be fruitful. Toward this end, we note several differences in honey bee methylation relative to vertebrate systems. First, methylation in vertebrates represses expression of repetitive DNAs and retrotransposons to maintain genome integrity, but in honey bees (and other insects) intermediate and high repetitive DNA elements and transposons are not methylated (*6*). This suggests that the role in mobile element repression has been lost or evolved after insects and vertebrates diverged (*6*, *9*). Second, overall levels of methylation appear to be lower in

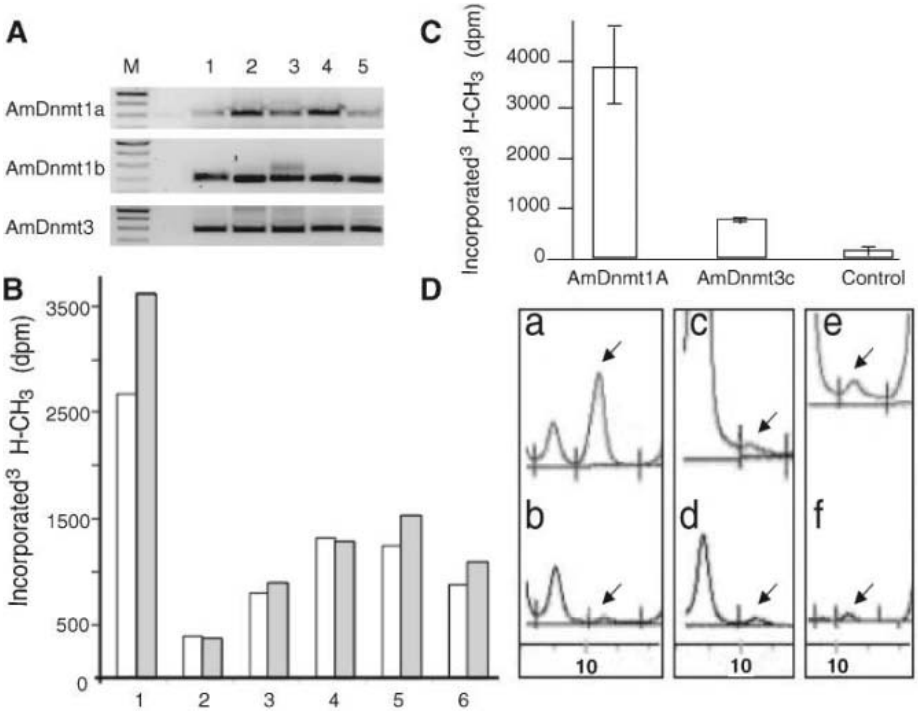

Fig. 1. DNA methylation in the honey bee. (**A**) Expression of *AmDNMT1* and *AmDNMT3* genes. Reverse transcription polymerase chain reaction (RT-PCR) of total RNA from multiple tissues and stages of development (24-hour-old embryo, adult worker ovary, queen larva, drone genitals and sperm, and adult worker brain; lanes 1 to 5, respectively) indicates expression of AmDnmt1a (top), AmDnmt1b (middle), and AmDnmt3 (bottom). Data are from a representative experiment repeated twice with similar results. For each experiment, total RNA was extracted from 50 eggs (24 hours old), one adult queen ovary, one queen larva, four adult drone genitals, and 10 brains from 8-day-old worker bees. *M* = 100–base pair ladder. (**B**) AmDNMT1A and AmDNMT3 proteins are catalytically active DNA methyltransferases in vivo. DNMT assays were performed on honey bee protein extracts prepared from either 40 embryos (lane 3), or 20 mg of tissue from 2-day-old, 3-day-old, or 5-day-old larvae (lanes 4 to 6, respectively). *Xenopus* egg extract (lane 1) was used as a positive control for DNMT activity, and bovine serum albumin (BSA) (lane 2) was used as a negative control. Experiments were carried out four times, each in duplicate, resulting in a highly reproducible pattern of activity. Results from a representative DNMT activity assay are shown. The two bars represent duplicates from one experiment. dpm, disintegrations per minute. (**C**) AmDNMT1 and AmDNMT3 proteins are catalytically active DNA methyltransferases in vitro. In vitro transcribed and translated full-length AmDNMT1A, AmDNMT3 catalytic domain (amino acid 401 to the carboxyl terminus) (AmDnmt3c), and empty vector (control) were analyzed for DNA methyltransferase activity using an unmethylated double-stranded DNA template. The average of three independent experiments (±SD) is shown. (**D**) Honey bee genome contains 5-methyl deoxycytosine. Genomic DNA from adult honey bees (a, b, d, and e), larvae (c), or rat liver (f), was digested to nucleotide monophosphates and analyzed by reverse phase high-performance liquid chromatography for dC^M. Digested bee DNA was spiked (a) with exogenous dC^M and analyzed in parallel with the digested DNA (b), clearly identifying a peak in adult honey bee coincident with dC^M enrichment (indicated by arrows). DNA from 3- to 4-day-old larvae (c) and adults (d) both contain dC^M. The dC^M peak from the larger sample (73.8 μg) of adult bee DNA (e) co-elutes with that from a lesser amount (17.8 μg) of rat liver DNA (f). The *x* axis is time (min) and the *y* axis is absorbance at 260 nm.

the honey bee than in vertebrates, arguing against DNA methylation as a global mediator of bee heterochromatin. Third, honey bees possess two paralogs for methylation maintenance, making them the first animal discovered to express multiple somatic DNMT1 proteins. Fourth, all detected methylation was limited predominantly to the coding regions of genes. It remains to be seen how any of these differences relate to the functions of methylation in social contexts.

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20. We thank J. Maleszka, T. Newman, K. Pruiett, and C. J. Schoenherr for technical assistance and D. C. Queller, C. J. Schoenherr, and members of the Jones and Robinson labs for reviewing the manuscript. Supported by the Illinois Sociogenomics Initiative (G.E.R.) and the Roy J. Carver Charitable Trust (C.A.M.), and a Consolider Ingenio 2010 program (CSD2006-49 from the Spanish Ministry of Education and Science (M.J. and M.A.P.). Sequences have been deposited into GenBank: AmDnmt1a (GB15130), AmDnmt1b (GB19865), AmDnmt2 (GB10767), AmDnmt3 (GB14232), and AmMBD (REFSEQ XP_392422). The authors declare no competing financial interests.

Supporting Online Material

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15 September 2006; accepted 3 October 2006
10.1126/science.1135213

From the Genome to the Proteome: Uncovering Peptides in the *Apis* Brain

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Neuropeptides, critical brain peptides that modulate animal behavior by affecting the activity of almost every neuronal circuit, are inherently difficult to predict directly from a nascent genome sequence because of extensive posttranslational processing. The combination of bioinformatics and proteomics allows unprecedented neuropeptide discovery from an unannotated genome. Within the *Apis mellifera* genome, we have inferred more than 200 neuropeptides and have confirmed the sequences of 100 peptides. This study lays the groundwork for future molecular studies of *Apis* neuropeptides with the identification of 36 genes, 33 of which were previously unreported.

The sequencing of the honey bee genome (*1*), as well as other current and planned sequencing projects, will not be accompanied by the extensive biochemical characterization that complemented the annotation processes for the *Drosophila melanogaster* and *Caenorhabditis elegans* genomes. This lack of biochemical information is particularly problematic when annotating neuropeptide genes, because neuropeptide protein precursors undergo extensive posttranslational processing before producing final neuropeptides. This makes the determination of the mature bioactive products from a genetic sequence, or even a protein precursor, challenging. Currently, there is no established methodology that permits rapid identification of the final neuropeptides from a nascent genome sequence.

Most efforts to elucidate neuropeptides from newly sequenced genomes have relied on homology searches to determine prohormone precursors, with follow-up biochemical studies to confirm the putative peptides. In *D. melanogaster* and *C. elegans*, hundreds of biochemical studies analyzing the neuropeptides of these two organisms had been performed before sequencing, providing enormous advantages when annotation of their genomes began (*2*). In 2002, through homology searches against the then–newly sequenced *Anopheles gambiae* genome, multiple neuropeptide precursor genes were reported, and from these precursors, the mosquito peptides were inferred (*3*). However, confirmation of these predictions and the discovery of the neuropeptides themselves have been left to follow-up studies that, for the most part, still need to be performed. In the *D. melanogaster* genome sequence, there is evidence for at least 31 neuropeptide genes (*4*–*6*), with a corresponding 32 genes predicted from the *A. gambiae* genome sequence (*3*). Prior studies of *Apis* neuropeptides reported three genes (*7*–*9*) and 15 neuropeptides identified with mass spectrometry (MS) (*7*, *10*); as shown in Table 1, the 36 neuropeptide-related genes

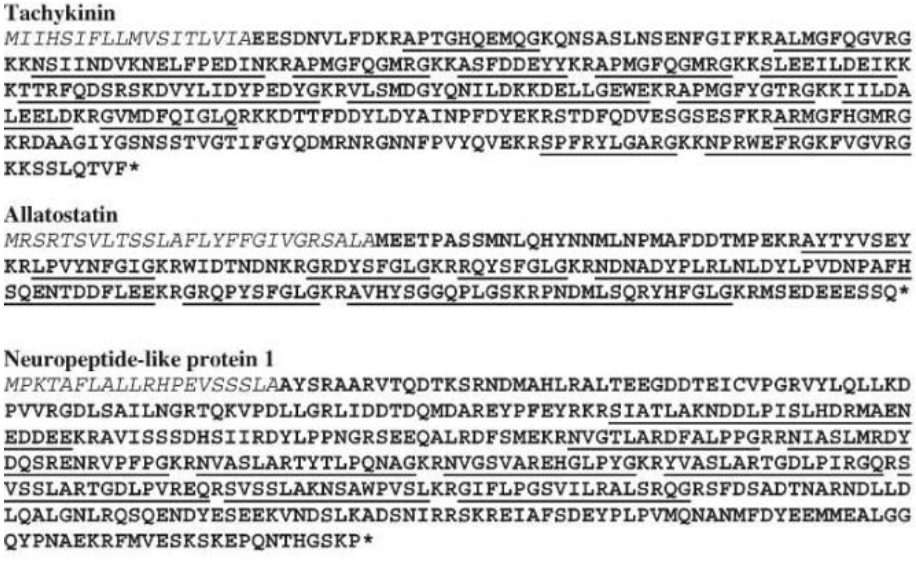

Fig. 1. Mass spectrometric sequence coverage for the tachykinin, allatostatin, and neuropeptide-like protein 1 prohormones. Sequences underlined indicate peptides that have been detected (and frequently sequenced) by mass spectrometry. The signal sequences for each prohormone are italicized.

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reported here are similar in number to those for the best-annotated animal genomes.

We combined homology and codon-scanning searches, together with techniques to confirm gene expression, in an iterative feedback loop to infer and to verify neuropeptide genes and their final peptide products (*11*). With this approach, a novel gene is annotated, the bioactive peptides predicted by a statistical algorithm developed in our laboratory (*12*), and the peptides confirmed through MS analysis of *Apis* brain samples. Alternatively, the characterization of a novel peptide by MS-driven de novo sequencing leads to targeted searches of the genome, followed by annotation of a new gene, which then is examined to predict additional novel peptides.

We discovered 13 unknown putative neuropeptides through de novo sequencing (table S1), which led to the identification of 11 genes that often encoded additional peptides. The original peptide, as well as the additional peptides discovered through identification of the precursor, frequently exhibited structural hallmarks of bioactivity—such as C-terminal amidation. In one instance, two intense signals corresponding to the closely eluting peptides, VPIYQEPRF and NVPIYQEPRF, were determined through MS sequencing of brain samples (*13*). When NVPIYQEPRF was used to probe the *Apis* genome, a gene was discovered that encodes this peptide. The peptide in the precursor was flanked by commonly used proteolytic cleavage sites. Additional peptides were predicted from the sequence by our statistically based prohormone-processing algorithm (*12*), and two of them (GYPYQHRLVY and SQAYDPYSNAAQFQLSSQSRGYPYQHRLVY) were subsequently identified with tandem MS (MS/MS) sequencing information, which confirmed their identities.

Table 1. *Apis mellifera* neuropeptide genes.

Gene name	Search method			Confirmation	
	MS	Homology search	Codon-scanning	qRT-PCR	MS
Adipokinetic hormone (AKH)		√			
Allatostatin (AST)	√	√	√	√	√
Apidaecin 1 and 2	√	√	√		√
Bursicon (BSN)		√			
Calcitonin-like diuretic hormone (DH31)	√	√			√
Corazonin (CRZ)	√	√			√
Crustacean cardioactive peptide (CCAP)		√		√	
Crustacean hyperglycemic hormone (ITP)		√		√	
Diuretic hormone (DH)		√			
Ecdysis-triggering hormone (ETH)		√			
Eclosion hormone (EH)		√		√	
FLRFamide-like			√		
IDLSRFYGHFNT-containing	√			√	√
Insulin		√		√	
ITGQGNRIF-containing	√				√
LRNQLDIGDLQ-containing	√				√
MVPVPVHHMADELLRNGPDTVI-containing	√				√
Myosuppressin	√	√			√
Neuropeptide F (NPF)		√			
Neuropeptide FF (NPFF)–like			√	√	
Neuroparsin		√			
Neuropeptide-like protein 1 (NPLP-1)	√	√	√	√	√
Neuropeptide-like protein 2 (NPLP-2)		√			
Neuropeptide-like protein 3 (NPLP-3)		√			
NVPIYQEPRF-containing	√			√	√
Orcokinin	√	√			√
Periviscerokinin (AFGLLTYPRIa-containing)	√				√
Pheromone biosynthesis–activating neuropeptide (PBAN)	√	√	√		√
Pigment-dispersing hormone (PDH)	√	√			√
RFamide-like1			√		
RFamide-like2			√	√	
Short neuropeptide F (sNPF)	√	√			√
SIFamide	√	√			√
Sulfakinin	√	√			√
Tachykinin (TK)	√	√	√		√
TWKSPDIVIRFa-containing	√				√

The transcript of this previously unannotated gene had been analyzed in microarray studies and was found to be highly correlated with behavioral plasticity in the honey bee (*14*). No homologs for the protein precursor were found in any of the sequenced eukaryotic genomes (*11*), although a section of the SQAYDPYSNAAQFQLSSQSRGYPYQHRLVY peptide had similarity to a portion of the β-tubulin protein from the fungi *Amanita sinensis* and from *Amanita pantherina* [SSRSRGYPYQHR for *A. sinensis* and SSKSRGYPYQHR for *A. pantherina*, BLAST Expect values (*E*-values) of 0.047 and 0.063].

Three precursors, discovered through de novo sequencing of peptides in *Apis* brain samples, and their corresponding peptides, LRNQLDIGDLQ, MVPVPVHHMADELLRNGPDTVI, and TWKSPDIVIRFamide, have no similarity to other known protein sequences or to any translated genome (*11*). In the case of the precursor encoding TWKSPDIVIRFamide, three additional predicted peptides have been identified, including one, GRNDLNFIRYamide, with a C-terminal amidation.

Another peptide de novo sequenced from *Apis* brain samples is ITGQGNRIF. Analysis of the *Apis* genome revealed a precursor encoding the peptide near the C terminus of the protein, situated between proteolytic cleavage sites. Proteins displaying similarities to this *Apis* peptide were present in *A. gambiae* and *D. melanogaster* [*A. gambiae* sequence: ENSANGP00000017235 (Ensembl gene database), *E*-value, $2E-50$; *D. melanogaster*: CG8216-PA, *E*-value, $5E-16$]. There is no predicted function for the *A. gambiae* precursor; the less similar *D. melanogaster* protein has a suggested role in DNA binding, as it is putatively involved in DNA transposition (FlyBase report CG8216). Most interesting, though, is that these putative proteins do not contain the ITGQGNRIF peptide detected in honey bee samples.

De novo MS sequencing with the support of the *Apis* genome also led to the discovery of multiple neuropeptides similar to other known insect neuropeptides (Table 1 and table S1). In total, 100 peptides from 20 precursor genes were detected by MS (tables S2 and S4), 87 of which had MS/MS sequence-confirming data. For most of these precursors, multiple peptides were characterized. In the cases of allatostatin, neuropeptide-like protein 1, and tachykinin, numerous peptides were sequenced or confirmed by mass matches, which resulted in high sequence coverage for the precursors (Fig. 1). In addition, we have confirmed precursors that, on the basis of homology, produce peptides with other functions (*11*).

However, because of variations that may be caused by organismal life cycles, analytical techniques, and/or sample sizes, biochemical-based approaches alone may not provide confirmation of some categories of neuropeptides. For example, eclosion hormones are expressed during short temporal windows and may not be detectable by

MS unless the timing of sample acquisition is matched to those windows. In cases where it was unlikely that the peptides would be detectable by MS, we characterized the proteins by bioinformatics approaches using the genomic data. Some of the well-known insect neuropeptide precursors that are predicted from the genome using homology-based searches include crustacean cardioactive peptide, crustacean hyperglycemic hormone, eclosion hormone, and insulin.

Because of the repetitive quality of several neuropeptide precursors, we developed a codon-scanning algorithm that searches for repetitive sequences in the genome. When multiple peptides are generated from a single precursor, they frequently share a repeating C-terminal amino acid pattern (for example, the FGLamide motif present in allatostatin peptides). Algorithms tailored to recognize repeating motifs can more successfully identify neuropeptide genes than traditional homology-based approaches. In an analysis of the *C. elegans* genome for RFamide-coding genes, two putative genes were identified by homology searches, a nominal number when compared with the 29 potential genes discovered with a tailored, pattern-matching algorithm (*15*). We used a similar approach to identify potential precursors without homologs in other species. As shown in Table 1, this method was also used to verify the positions in the genome of several of the repeating precursors, for example, allatostatin, tachykinin, and pheromone biosynthesis–activating neuropeptide.

As mentioned above, one neuropeptide gene family containing repeating C termini, the RFamides, is a well-studied family of myotropic peptides that have been identified in many species ranging from mollusks to mammals (*16*–*20*). In mammals, two of the RFamides, neuropeptides FF (NPFF) and AF (NPAF), are produced from NPFF precursors and end in a C-terminal motif, QRFamide (*21*). We probed the *Apis* genome using the codon-scanning algorithm looking for an open reading frame that encodes a motif with at least two RFamides located within 1 kilobase of each other. We discovered a putative gene that encoded a signaling protein containing three peptides terminating in QRFamide. In this particular case, the codon-scanning algorithm was the singular approach in our platform able to identify this previously unreported gene; expression of this putative *Apis* NPFF-like gene was verified by quantitative reverse transcription–polymerase chain reaction (qRT-PCR) (table S3). We also identified three additional RFamide neuropeptide genes—FLRFamide, RFamide1, and RFamide2. Because these precursors do not display significant similarity to RFamide precursors from other insects, they are not identifiable using homology searches.

Our combined approach yields many more peptides than the individual approaches used previously. As a result, in a single investigative effort, a comparable number of neuropeptides are now known in the honey bee relative to other well-studied animal models. Microarrays can be designed to include a greater number of neuropeptide gene products, thereby expanding our understanding of the expression of the neuromodulators inherent to the operation of neuronal networks. The potential of our blended technology approach to facilitate discovery of these peptides is not only significant for advancing honey bee research, it demonstrates promise for neuropeptide discovery in the large number of other new genomes currently being sequenced.

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23. We dedicate this article to A. De Loof for a full career of insect research at the K. U. Leuven. We thank T. Newman for assistance with qRT-PCR, B. Southey for aiding our BLAST searches, and C. Whitfield for helpful discussions. We acknowledge M. Corona for annotating the insulin gene. Supported by the National Institutes of Health through NS31609, P30 DA01830 (J.V.S.), GM068946 (S.L.R.-Z.), and DC006395 (G.E.R.). P.V., G.B., J.H., and E.V. are postdoctoral researchers of the FWO-Flanders (Fund for Scientific Research–Flanders), supported by FWO-Grant G.0444.05.

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5799/647/DC1
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21 December 2005; accepted 27 July 2006
10.1126/science.1124128

Bacterial Taxa That Limit Sulfur Flux from the Ocean

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Flux of dimethylsulfide (DMS) from ocean surface waters is the predominant natural source of sulfur to the atmosphere and influences climate by aerosol formation. Marine bacterioplankton regulate sulfur flux by converting the precursor dimethylsulfoniopropionate (DMSP) either to DMS or to sulfur compounds that are not climatically active. Through the discovery of a glycine cleavage T-family protein with DMSP methyltransferase activity, marine bacterioplankton in the Roseobacter and SAR11 taxa were identified as primary mediators of DMSP demethylation to methylmercaptopropionate. One-third of surface ocean bacteria harbor a DMSP demethylase homolog and thereby route a substantial fraction of global marine primary production away from DMS formation and into the marine microbial food web.

Marine phytoplankton synthesize DMSP for use as an osmolyte (*1*), predator deterrent (*2*), and antioxidant (*3*). The degradation of DMSP to DMS and subsequent exchange of DMS across the ocean-atmosphere boundary is the main natural source of sulfur to the atmosphere, amounting to ~20 Tg of sulfur annually (*4*). DMS-derived atmospheric sulfur affects cloud formation and the radiative properties of Earth (*5*). Phytoplankton are known to degrade DMSP to DMS, but efforts to predict global patterns of ocean-atmosphere DMS flux based solely on phytoplankton parameters have been unsuccessful (*6*). Other members of the marine plankton must therefore influence the production and emission of DMS from the surface ocean (*7*).

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Marine bacterioplankton are known to degrade DMSP by a pathway that first converts DMSP to methylmercaptopropionate (MMPA) in a demethylation reaction, and subsequently to methanethiol (MeSH) (*8*) or mercaptopropionate (MPA) (fig. S1) (*9*). The first step of this alternative pathway is crucial to oceanic sulfur emissions, because it removes a methyl group from DMSP and eliminates DMS as a possible degradation product. Furthermore, some of the MMPA-derived sulfur is incorporated subsequently into bacterial amino acids (*10*) and, through trophic transfers, into the marine microbial food web. Despite the estimated 50 to 90% of DMSP that is metabolized by marine bacterioplankton through this pathway (*11*, *12*), the taxa that mediate DMSP demethylation in ocean surface waters are unknown.

Bacteria in the marine Roseobacter clade have been shown to demethylate DMSP in culture (*8*). *Silicibacter pomeroyi* DSS-3 (*13*) performs both DMSP demethylation to MeSH and DMSP cleavage to DMS (*10*). A 20,000-member Tn*5*-based transposon insertion library of *S. pomeroyi* was screened for interruption of MeSH formation based on failure to produce a thiol from DMSP, and phenotypes of potential mutants were monitored by analysis of sulfur gas formation. A mutant unable to make MeSH yet able to produce DMS at wild-type levels had a transposon insertion in SPO1913 (Fig. 1), a gene encoding a protein in the glycine cleavage T-protein family (Pfam PF01571, Enzyme Commission number 2.1.2.10). DMSP degradation to MeSH was restored by complementation of the mutant in trans with an intact SPO1913 gene (fig. S2). Enzyme assays in cell-free extracts of wild-type and mutant strains showed that SPO1913 encodes the protein responsible for the first step in MeSH formation: the demethylation of DMSP to MMPA (Table 1). This DMSP demethylase gene was designated *dmdA*.

Table 1. DMSP demethylase activity in *S. pomeroyi* and *E. coli* strains with or without functional *dmdA* genes (SPO1913 or SAR11_0246) measured as MMPA formation (nmol min^{-1} mg $protein^{-1}$) in cell-free extracts. Activity in wild-type extracts was linear with both time and amount of protein, dependent on the presence of DMSP and the coenzyme tetrahydrofolate (THF), and comparable to the rate of MeSH production by whole cells. The limit of detection was 0.02 to 0.05 nmol min^{-1} mg $protein^{-1}$. Activity is shown ± SD.

Source of extract	DMSP:THF demethylase activity
S. pomeroyi DSS-3, wild-type	0.15 ± 0.02
S. pomeroyi mutant 41-H6, Tn*5* inactivation of SPO1913	0
E. coli with pABX101, recombinant SAR11_0246	0.24 ± 0.05
E. coli with pCYB1, vector alone	0

Basic Local Alignment Search Tool (BLAST) searches of genome sequences of other cultured bacteria yielded only two complete *dmdA* orthologs in any non-Roseobacter genome. Both were from marine bacteria in the SAR11 clade, *Pelagibacter ubique* HTCC1062 (*14*) and *P. ubique* HTCC1002 (*15*) (Fig. 1). One other partial *dmdA* sequence (Fig. 1) was found on a small (1.4-kb) fragment of environmental DNA contaminating the genome sequence of the sea ice bacterium *Psychroflexus torquis* (*15*); the taxonomic origin of this sequence is unknown (*16*).

We searched marine metagenomic libraries to determine whether *dmdA*-like sequences were present in natural bacterial communities. In the Sargasso Sea (*11*), *dmdA* homologs were sufficiently abundant to be harbored by about a third of bacterioplankton cells (Table 2). The Sargasso sequences formed four clades distinct from other glycine cleavage T-protein family proteins (Fig. 2). Clade A sequences clustered with DMSP demethylases from *S. pomeroyi* and other Roseobacters (table S1). Based on the number of clade A homologs relative to Roseobacter-like 16*S* rDNA sequences (*13*), at least 80% of Roseobacters captured in the Sargasso Sea metagenome possess a *dmdA* homolog. Sequences similar to clade B and clade C were not found among cultured bacteria; these sequences may be from uncultured or unsequenced marine bacterial lineages, or they may represent sequence diversity within the known *dmdA*-containing taxa. Clade D sequences clustered with the *dmdA* orthologs from *P. ubique* HTCC1062 and HTCC1002. Two sequence assemblies from the Sargasso Sea that contained clade D homologs showed similar gene organization and highest gene similarities to the *P. ubique* genomes (Fig. 1). Based on the number of clade D homologs relative to SAR11-like 16*S* rDNA sequences (*13*), only 40% of SAR11 cells demethylate DMSP; these may belong to an ecologically distinct subgroup within the taxon (*17*).

Genes adjacent to *dmdA* homologs were consistent within a clade but differed across clades (Fig. 1). Previous studies have shown that MMPA can be metabolized to MeSH or MPA in seawater (fig. S1) (*9*, *18*). Thus, whereas all DMSP demethylating taxa must have *dmdA* in common, a different, taxon-specific suite of genes may encode for the subsequent metabolism of MMPA (Fig. 1).

Although sequence coverage is small compared with that of the Sargasso Sea data set (Table 2), other marine metagenomic databases contain evidence of DMSP demethylase genes.

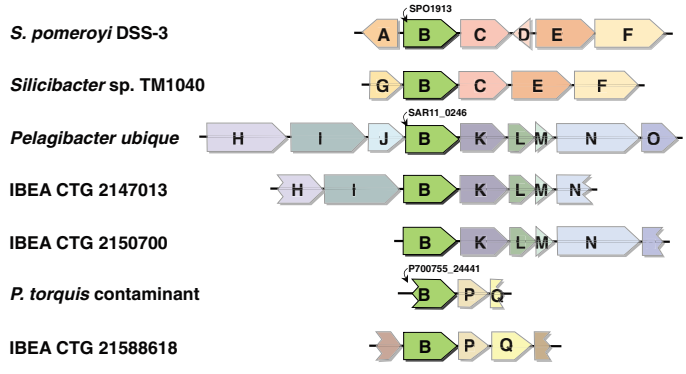

Fig. 1. Gene neighborhoods of cultured marine bacteria and selected Sargasso Sea contigs (labeled as IBEA CTG) harboring *dmdA* genes. Representative sequences that assembled into the Sargasso Sea contigs (i.e., with >97% identity) are indicated on Fig. 2. The *P. torquis* contaminant *dmdA* is a partial sequence on a small genome fragment. A, GntR family transcriptional regulator; B, glycine cleavage T-family protein (*dmdA*); C, dehydrogenase; D, glyoxalase family protein; E, aminotransferase class V; F, deoxyribodipyrimidine photolyase (*phrB*); G, protein of unknown function; H, acyl coenzyme A (CoA) dehydrogenase; I, acyl CoA synthase; J, hydrolase (*mhpC*); K, aspartate semialdehyde dehydrogenase; L, succinate dehydrogenase cytochrome b (*sdhC*); M, membrane protein; N, succinate dehydrogenase (*sdhA*); O, succinate dehydrogenase Fe-S protein; P, OsmC-like protein; Q, enoyl-CoA hydratase/isomerase.

Table 2. Abundance of *dmdA* homologs in marine bacterioplankton metagenomic surveys. Sargasso Sea data are from surface seawater samples (Stations 1 to 7) using the unassembled shotgun library (*11*). Station Aloha data are grouped into photic zone (10, 70, and 130 m) and deep water (500, 770, and 4000 m) samples according to DeLong *et al*. (*19*). Sapelo Island data are from surface seawater samples (0.5 m). *recA* homologs were determined by BLAST analysis using the *E. coli recA* sequence as the query. The percentage of cells with *dmdA* was calculated as *dmdA* × 100/*recA*. *recA* is an essential single-copy gene. Mbp, mega–base pairs.

	Library size (Mbp)	*dmdA* homologs					*recA* homologs	% of cells with *dmdA*
		Clade				Total		
		A	B	C	D			
Sargasso Sea (oceanic)	1626	29	18	83	247	377	1029	37
Station Aloha (oceanic) photic zone	24.8	1	0	0	1	2	5	40
Station Aloha (oceanic) deep water	31.1	0	0	0	0	0	17	0
Sapelo Island (coastal)	15.2	9	0	0	1	10	26	38

Two *dmdA* homologs were found in photic zone samples from the Pacific Station Aloha database (*19*); as expected, none were in the deep water samples from this site where DMSP flux is negligible. Ten *dmdA* homologs were found in a metagenome from southeastern U.S. coastal water. Similar to the Sargasso Sea metagenome, the abundance of *dmdA* homologs in both these samples indicated that about a third of bacteria in surface ocean waters may participate in DMSP demethylation (Table 2).

The marine metagenomic surveys indicated that the majority of environmental *dmdA* homologs belonged to clades for which DMSP demethylase activity has not been experimentally verified (Table 2). To address this issue, the *P. ubique* HTCC1062 *dmdA* (gene SAR11_0246) was synthesized and introduced in trans into *Escherichia coli*. Cell-free extracts of the recombinant *E. coli* formed MMPA from DMSP (Table 1), confirming demethylation by a protein in the largest environmentally occurring clade (clade D).

DMSP synthesis is estimated to account for ~1 to 10% of global marine primary production (*20*), consistent with previous evidence that a large fraction of active marine bacteria assimilate sulfur from DMSP (*21*, *22*) and the wealth of DMSP demethylation genes we found in surface water bacterioplankton communities. The evidence that oceanic *dmdA* homologs are most similar to those from cultured SAR11 bacteria (50 to 65%, Table 2), whereas coastal homologs are most similar to those from cultured Roseobacters (90%), is consistent with known differences in the ecology and distribution of these two abundant bacterioplankton groups (*13*, *14*). This evidence further suggests that SAR11 bacteria may dominate demethylation in the open ocean, where DMSP concentrations are low (10 to 15 nM) and relatively constant, whereas Roseobacters may dominate in phytoplankton blooms and coastal regions, where DMSP concentrations are high (up to 100 nM) and more variable. Knowledge of the kinetic and ecological diversity of bacterial DMSP demethylases represented by these major marine taxa is critical to understanding both the routing of reduced carbon and sulfur into the microbial food web and the bacterial controls on ocean-atmosphere sulfur flux with consequences to global climate regulation.

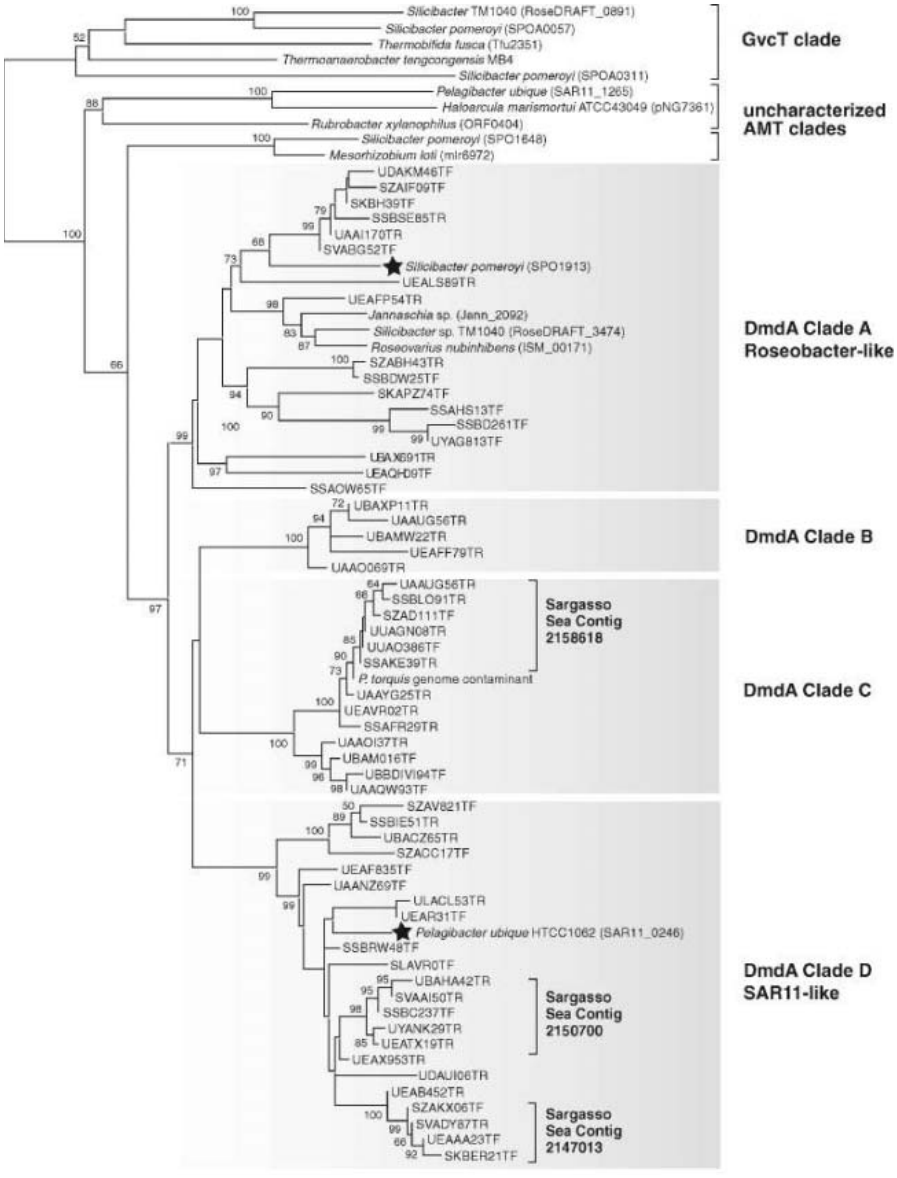

Fig. 2. Minimum evolution phylogenetic tree of amino acid sequences of glycine cleavage T-protein (GcvT) family proteins, including DmdA and related aminomethyltransferases (AMT). Sequences from cultured bacteria are labeled with organism name and gene designation. Selected Sargasso Sea metagenomic library sequences are identified by sequence identification and, if applicable, a contig designation. Proteins with confirmed DMSP demethylase activity are marked with a star. Percentage of 100 bootstrap samples supporting each node are shown if >50.

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20. On the basis of global emissions of DMS ranging from 0.47 to 1.03 Tmol per year (*4*) and the assumption that DMS emissions represent 1 to 4% of gross DMSP production, we estimated a global DMSP production rate of 11.7 to 103 Tmol of sulfur per year. Because each mole of DMSP contains 5 mol of carbon, the gross global DMSP production is 58.6 to 516 Tmol of carbon per year. With a global marine primary production of 3750 Tmol of carbon per year (*23*), 1.3 to 13.8% is in the form of DMSP. Similar contributions to marine carbon production can be estimated from DMSP:chlorophyll *a* and assumed C:chlorophyll *a* ratios (*12*).
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24. We thank P. Capes, R. Hein, and S. Napierala for technical assistance; K. Remington and S. Sun for bioinformatics assistance; R. Belas and E. Stabb for advice on genetic techniques; J. Wiegel for equipment access; J. Mou for access to Sapelo Island metagenomic data; and C. English for graphics support. This project was funded by grants from NSF (MCB-0315200 to M.A.M., W.B.W., and R.P.K.) and the Gordon and Betty Moore Foundation (to M.A.M.). Accession numbers: *dmdA*

sequences are available at NCBI under accession numbers AAV95190 (*S. pomeroyi*), ABF64177 (*Silicibacter* sp. TM1040), ABD55296 (*Jannaschia* sp. CCS1), EAP76657 (*Roseovarius nubinhibens* ISM), AAZ21068 (*P. ubique* HTCC1062), EAS85076 (*P. ubique* HTCC1002), EAS69357 (*P. torquis* genome sequence contaminant), DU750654 and DU737812 (Station Aloha metagenome), and DQ874604-DQ874613 (Sapelo Island metagenome).

Supporting Online Material
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Figs. S1 and S2
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31 May 2006; accepted 19 September 2006
10.1126/science.1130657

Dimethylsulfoniopropionate Uptake by Marine Phytoplankton

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Dimethylsulfoniopropionate (DMSP) accounts for most of the organic sulfur fluxes from primary to secondary producers in marine microbial food webs. Incubations of natural communities and axenic cultures with radio-labeled DMSP showed that dominant phytoplankton groups of the ocean, the unicellular cyanobacteria *Prochlorococcus* and *Synechococcus* and diatoms, as well as heterotrophic bacteria take up and assimilate DMSP sulfur, thus diverting a proportion of plankton-produced organic sulfur from emission into the atmosphere.

Dimethylsulfoniopropionate (DMSP) is synthesized by ubiquitous phytoplankton taxa as a solute, probably for osmoregulatory and antioxidant purposes (*1*–*4*). DMSP is the precursor of the climate-active gas dimethylsulfide (DMS), the main natural source of sulfur to the global atmosphere and a major aerosol and cloud droplet precursor over the ocean (*5*–*7*). Enzymatic cleavage of DMSP into volatile DMS is the fate of only a fraction (generally <50%) of all DMSP produced (*8*). Recent research has revealed that algal DMSP plays an important role in food-web processes supplying sulfur and carbon to heterotrophic bacteria and, to a lesser extent, to microzooplankton herbivores (*9*–*12*). Thus, the biogeochemical fate and function of DMSP is largely determined by a switch between conversion into DMS and sulfur assimilation by microorganisms, which in turn depends on the composition, structure, and dynamics of the planktonic food web. The ability to assimilate DMSP sulfur seems to be widespread among taxa of heterotrophic bacterioplankton (*13*, *14*) and has also been observed in the cyanobacterium *Synechococcus* (*15*). Our work aimed to find out whether major non-DMSP–producing phytoplankton also assimilate DMSP sulfur.

To investigate the distribution of DMSP sulfur uptake and assimilation among picoplankton, we used flow cytometry cell sorting and measured assimilation by picophototrophs and heterotrophic bacteria by using radio-labeled DMSP. Surface seawater samples were collected from the coasts of the Gulf of Mexico, the northwest Mediterranean, and Gran Canaria Island and from the Sargasso Sea. After light and dark incubations with [^{35}S]DMSP, sample aliquots were passed through the flow cytometer and sorted into four major groups: heterotrophic bacteria, *Prochlorococcus*, *Synechococcus*, and autofluorescent picoeukaryotes. All groups showed some capability for assimilating DMSP sulfur (Fig. 1). The most notable DMSP sulfur assimilators were heterotrophic bacteria, followed by *Prochlorococcus*, *Synechococcus*, and picoeukaryotes. Incubation of samples in the light stimulated DMSP sulfur assimilation by picophototrophs by as much as a factor of 2.2. The phototrophs accounted for 10 to 34% of picoplanktonic DMSP consumption in the light, with the remaining 66 to 90% being carried out by heterotrophic bacteria.

Until now the only phototrophs for which DMSP use had been observed were *Synechococcus*. It seems that, in a similar way to that of heterotrophic bacteria (*10*) and *Synechococcus* (*15*), *Prochlorococcus* may also benefit from using a reduced sulfur source such as DMSP, probably by saving the energy required to reduce sulfate. Studies with cultured and natural assemblages of heterotrophic bacteria have provided evidence for a common membrane transporter for DMSP and glycine betaine (GBT) (*16*, *17*), and, interestingly, putative GBT transporter genes have been found in the genome of *P. marinus* MIT9313 (*18*).

In one of the samples (Gran Canaria Island), eukaryotic picophytoplankton also showed significant incorporation of ^{35}S from [^{35}S]DMSP (Fig. 1). It is possible, however, that some of these eukaryotes were mixotrophic bacterivores that had fed on ^{35}S-radio-labeled bacteria.

We used microautoradiography with [^{35}S]DMSP to follow DMSP sulfur assimilation by organisms larger than 5 μm collected during an annual time series in the coastal Mediterranean. Consistent with our flow-cytometric observations of picoeukaryotes, many phytoplankton cells, including dinoflagellates, cryptophytes, and diatoms, became radio-labeled (Fig. 2). Mixotrophy by bacterivory has been described for dinophytes, cryptophytes, and haptophytes (*19*), but not for diatoms, which consequently must have directly taken up ^{35}S from dissolved radio-labeled DMSP.

The DMSP-to-chlorophyll (DMSP:chl-*a*) ratio is a good indicator of how strong a DMSP producer a phytoplankton assemblage is and how much of the available carbon and sulfur are accounted for by DMSP (*9*, *11*). We found that the proportion of diatoms that had assimilated [^{35}S]DMSP sulfur followed a pattern very similar to that of independently measured DMSP:chl-*a* ratios from parallel samples (Fig. 3) through the annual course of sampling, with highest values observed in June and August. In other words, higher numbers of DMSP sulfur–assimilating diatoms did not occur when these phytoplankters were more abundant (late winter) but when DMSP was more abundant with respect to total sulfur and carbon fluxes (summer).

DMSP is a zwitterion that cannot cross cell membranes without a specific transporter (*17*). DMSP sulfur assimilation by diatoms implies, therefore, that either these algae have a DMSP transport system or they were taking up by-

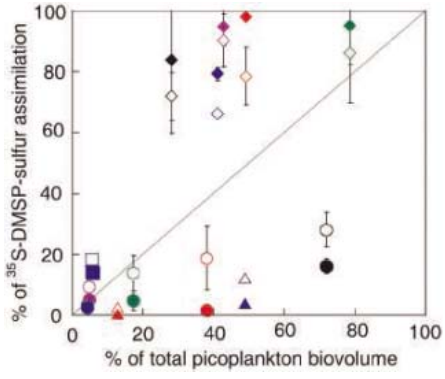

Fig. 1. Contribution of different groups of picoplankton to total picoplankton [^{35}S]DMSP assimilation versus their contribution to the total picoplankton biovolume. Solid and open symbols correspond to dark and light incubations, respectively (diamonds, heterotrophic bacteria; circles, *Synechococcus*; squares, *Prochlorococcus*; and triangles, picoeukaryotes). Green, Blanes Bay (northwest Mediterranean); black, off Dauphin Island (Gulf of Mexico); purple, Sargasso Sea; red, Pensacola beach (Gulf of Mexico); and blue, Gran Canaria Island. Error bars represent standard deviation of the mean (*n* values from 2 to 6). The 1:1 line is included as a reference.

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products of [^{35}S]DMSP degradation by bacteria, such as [^{35}S]methanethiol. To check for the capability of diatoms to take up DMSP, we grew two axenic strains of the centric diatoms *Thalassiosira pseudonana* (CCMP1335) and *T. oceanica* (CCMP1005). We chose these two species for their low cellular DMSP content (1.3 and 0.9 mM, respectively) and their small size [circa (ca.) 5 and 8 μm diameter, respectively].

After 12 hours of incubation with trace concentrations of [^{35}S]DMSP, both species had taken up most of it. Contrasting with what was observed with picophototrophs, light only stimulated uptake by ~10% in diatoms (Fig. 4). When nonlabeled DMSP was added at a concentration of 10 μM, the uptake of [^{35}S]DMSP was almost completely suppressed. Addition of 10 μM of nonlabeled GBT produced the same effect (Fig. 4, top). Trace amounts of [^{14}C]GBT were taken up by both species, and, likewise, when 10 μM of nonlabeled GBT was added, [^{14}C] GBT uptake was suppressed. Addition of 10 μM of DMSP inhibited ^{14}C-GBT uptake by half in *T. pseudonana* and by a third in *T. oceanica* (Fig. 4, bottom). The two species of *Thalassiosira* seemed to use the same transport system for both compounds, in a way similar to that of heterotrophic bacteria (*16*, *17*). Genes encoding for a putative GBT membrane transporter have been found in the genome of this same *T. pseudonana* CCMP1335 strain (*20, 21*).

Our results provide evidence that diatoms and the two major groups of pelagic nonfilamentous cyanobacteria can take up and use DMSP. Production of DMSP, although ubiquitous in the ocean, is taxon dependent and, to some extent, size dependent too: Small haptophytes and dinoflagellates are generally high producers, whereas diatoms (except for those that grow in sea ice) and cyanobacteria are low or nonproducers (*22–24*). Tests with two axenic strains of the haptophyte *Emiliana huxleyi* (CCMP373 and CCMP374) and the dinoflagellate *Karenia brevis* (CCMP 2281), strong and moderate DMSP producers, respectively, revealed no uptake of [^{35}S]DMSP (table S2).

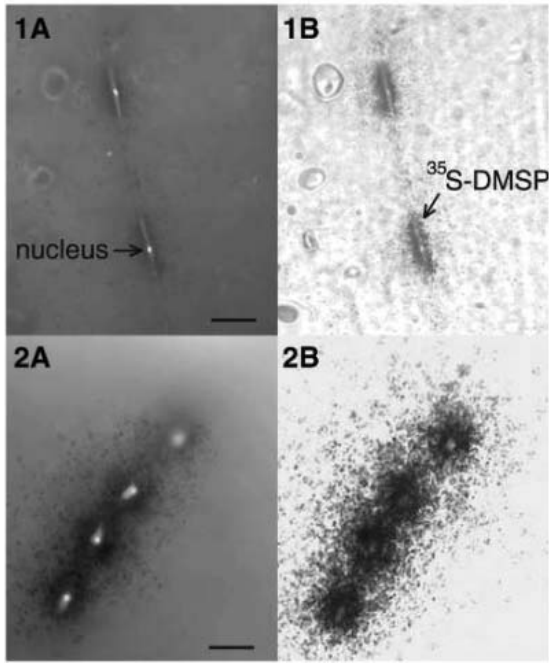

Fig. 2. Photomicrographs of two species of diatoms, (1) *Pseudo-nitzschia* sp. and (2) *Chaetoceros* sp. occurring in a natural phytoplankton assemblage from Blanes Bay (northwest Mediterranean), after being processed by microautoradiography. (**A**) Epifluorescence micrographs under UV light, showing 4′,6′-diamidino-2-phenylindole–stained nuclei. (**B**) Same cells observed under transmitted light. Black dots surrounding cells indicate assimilation of [^{35}S]DMSP by diatoms. Scale bars indicate 10 μm.

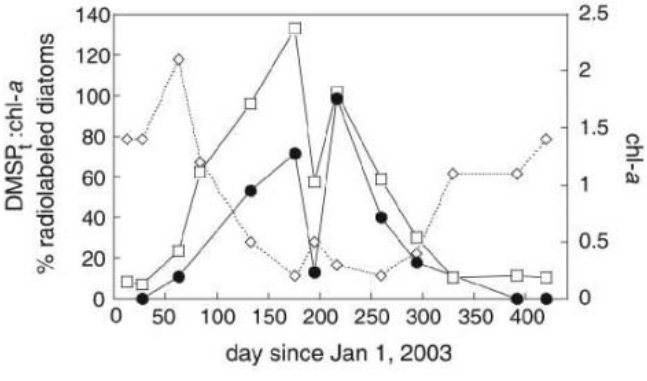

Fig. 3. Annual variation of the percentage of DMSP sulfur–assimilating diatoms (circles) and the in situ DMSP:chl-*a* ratio in nmol•μg^{-1} (squares) in surface waters of Blanes Bay (northwest Mediterranean). Chl-*a* concentration (μg•l^{-1}) is also shown (diamonds).

Our results thus suggest that low- or non–DMSP-producing diatoms and cyanobacteria consume DMSP released by high-producing phytoplankton partners.

But what is the quantitative relevance of this process in nature? *Prochlorococcus* are numerically the dominant phytoplankters in the oligotrophic central oceanic gyres and tend to be replaced by *Synechococcus* in productive tropical waters and in the transitional zones to temperate waters (*25*). Both co-occur in the euphotic zone with small high-DMSP–producing eukaryotic algae. In upwelling regions and in waters that receive pulses of nutrients from continental discharges or from episodic or seasonal mixing, diatoms grow among a background of small algae and tend to dominate primary production (*26*). We have shown that picophototrophs contributed 10 to 34% of DMSP sulfur assimilation in the light-exposed waters studied. The contribution of total phytoplankton (including diatoms) is harder to quantify. Size-fractionated DMSP-sulfur assimilation experiments conducted in the surface Sargasso Sea in April 2002 and July 2004 revealed that, in the dark, 100% of the DMSP sulfur assimilation was carried out by microorganisms smaller than 0.6 μm (i.e., mostly heterotrophic bacteria), whereas, in the light, assimilation was stimulated by two- to threefold; 50 to 70% of the total assimilation was by organisms larger than 0.6 μm (i.e., mostly phototrophic prokaryotes and all eukaryotes).

All of our incubations were conducted in the absence of ultraviolet (UV) radiation; hence, it is likely that we are underestimating the relative contribution of phytoplankton (UV-protected by pigments) versus heterotrophic bacterioplankton as DMSP sulfur sinks. In any case, phytoplankton DMSP utilization confirms a major role of DMSP as a carrier for sulfur and carbon through multiple levels of marine microbial food webs (*9*, *11*). Ours results show that, in the illuminated conditions of the surface ocean, phytoplankton assimilate DMSP sulfur in similar proportions to heterotrophic bacterioplankton, both together assimilating ca. 20% of total DMSP consumption. If we also include the assimilation by microzooplankton (ca. 20%), then the total assimilative consumption by microbial food web components is of similar magnitude to DMS production (ca. 10 to 50% of total DMSP turnover) and much higher than eventual DMS ventilation to the atmosphere (ca. 3%) (fig. S1). Assimilation of DMSP, therefore acts to regulate sulfur emissions into the atmosphere, with potential important consequences to the global biogeochemical sulfur cycle and climate (*5*, *7*).

Another broad implication of our results refers to the use of organic substrates by phytoplankton. Our data add to previous observations (*15*, *27–29*) to demonstrate that widespread and numerically dominant phytoplankton groups are capable of taking up essential elements in reduced organic forms. This, together with the phagotrophic bacterivory described in many algal

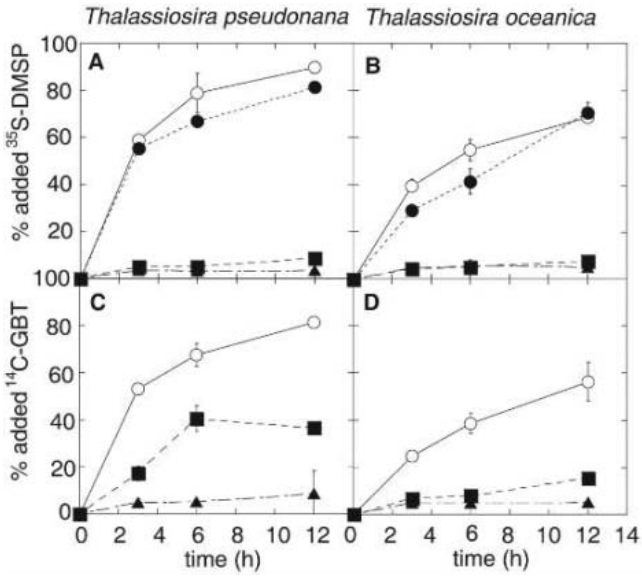

Fig. 4. (**A** to **D**) Uptake of [^{35}S]DMSP (top, circles) and [^{14}C]GBT (bottom, circles) by axenic cultures of *T. pseudonana* (left) and *T. oceanica* (right). Solid and open symbols correspond to dark and light incubations, respectively. Time series of isotope uptake in the presence of potential competitive inhibitors, 10 μM of non–radio-labeled DMSP (squares), and 10 μM GBT (triangles) are also shown. Error bars correspond to standard deviation from triplicate measurements.

taxa (*19*, *30*), further reveals how metabolically versatile phytoplankton are as a fundamental ecological player in the ocean and how challenging it becomes to implement their dynamics in oceanic biogeochemical models.

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31. We thank C. Pedrós-Alió for providing microautoradiography advice and critical discussions, J. M. González for assistance with the *Prochlorococcus* genome, F. Unrein and L. Arín for help with the identification of phototrophic cells under the microscope, and E. Blanch and J. Felipe for assistance with flow cytometry cell sorting. This research was supported by the European Union through project Bacterial Single-Cell Approaches to the Relationship Between Diversity and Function in the Sea (BASICS, EVK3-CT-2002-00078), by the Spanish Ministry of Education and Science through projects Relevancia de la diversidad microbiana filogenética y de estados fisiológicos para los procesos biogeoquímicos marinos (MicroDiFF, REN2001-2120/MAR to J.M.G.) and Ciclo del Azufre en el Oceano Superficial (CAOS, CTM2004-20022-E to R.S.) and a Ph.D. studentship to M.V.-C., and by a Catalan government grant (2005SGR00021 to R.S.).

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5799/652/DC1
Materials and Methods
Fig. S1
Tables S1 and S2

8 June 2006; accepted 19 September 2006
10.1126/science.1131043

A Centrosome-Independent Role for γ-TuRC Proteins in the Spindle Assembly Checkpoint

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The spindle assembly checkpoint guards the fidelity of chromosome segregation. It requires the close cooperation of cell cycle regulatory proteins and cytoskeletal elements to sense spindle integrity. The role of the centrosome, the organizing center of the microtubule cytoskeleton, in the spindle checkpoint is unclear. We found that the molecular requirements for a functional spindle checkpoint included components of the large γ-tubulin ring complex (γ-TuRC). However, their localization at the centrosome and centrosome integrity were not essential for this function. Thus, the spindle checkpoint can be activated at the level of microtubule nucleation.

The classical function of the centrosome is the organization of microtubules in higher eukaryotic cells. Its duplication and function are tightly integrated into cell cycle regulatory processes (*1*, *2*). A role for the centrosome in the spindle assembly checkpoint, as an essential guardian of cell cycle progression, has been suggested but not established on the molecular level (*3*). γ-tubulin is a highly conserved component of the microtubule-organizing center (MTOC) in most animal cells and is involved in the initiation of microtubule nucleation (*4*, *5*). γ-tubulin is mainly found in two complexes: the large γ-tubulin ring complex (γ-TuRC) (comprising Grip71, Grip75, Grip84, Grip91, Grip128, Grip163, and γ-tubulin in *Drosophila*) and its subunit, called the γ-tubulin small complex (γ-TuSC) (comprising Grip84, Grip91, and γ-tubulin) (*6*, *7*). γ-TuRC promotes the nucleation of a microtubule filament (*4*, *6*, *8*). In addition, γ-tubulin is thought to be required for a G_1-related checkpoint pathway and spindle formation (*9*–*12*). Finally, the centrosome-associated fraction of γ-tubulin ring proteins is essential for coordinating mitotic events (*13*–*15*).

We investigated the role of core centrosomal proteins such as γ-TuRC proteins and centrosomin (cnn) (*16*) in spindle checkpoint activation in *Drosophila* cells (supporting online material text) by depleting target proteins using RNA interference (RNAi) (*17*) (Fig. 1). We focused on the analysis of the γ-TuSC components γ-tubulin and Grip84, the γ-TuRC component Grip71, and the

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centrosomal core protein cnn, which is not part of the γ-TuRC. Cells were transfected with double-stranded RNA (dsRNA) for these components and for enhanced green fluorescent protein (EGFP) as a negative control and were harvested for immunofluorescence microscopy and immunoblotting experiments. The RNAi experiments reduced the levels of target proteins (Grip71, γ-tubulin, and cnn) by >90% (Fig. 1A). The cells treated with dsRNA for Grip84, Grip71, and γ-tubulin showed a clear increase in the number of mitotic cells as opposed to the control cells (Fig. 1B). In contrast, the mitotic index of cells depleted of cnn did not significantly differ from that of the control cells (Fig. 1B).

To elucidate possible mechanisms of mitotic arrest, we defined defects in spindle morphology and microtubule organization. Normal bipolar biastral microtubule organization was observed in control cells (Fig. 1, C and D). The cells treated with dsRNA for γ-tubulin and Grip84 exhibited bipolar monastral (Fig. 1, E and F) and monopolar anastral (Fig. 1G) spindle organization with metaphase-like chromosome arrangements. Cells in the γ-TuRC knockdown experiments predominately formed spindles with one centrosome (Fig. 1, E to G). In contrast, cnn depletion led to anastral bipolar spindle arrangements, with anastral poles that were frequently barrel-shaped and unfocused (Fig. 1, H and I). This observation indicated the absence of intact mitotic centrosomes, as verified by immunofluorescence microscopy (Fig. 1, H and I). In spite of these abnormalities, anaphase progressed normally in cnn-depleted cells (Fig. 1H) without an increase of abnormal chromosome arrangement when compared to control cells. This finding is consistent with the fact that the removal of centrosomes does not prevent cells from building a functional spindle and progressing to anaphase (*18*–*20*). Thus, the depletion of γ-TuRC compo-

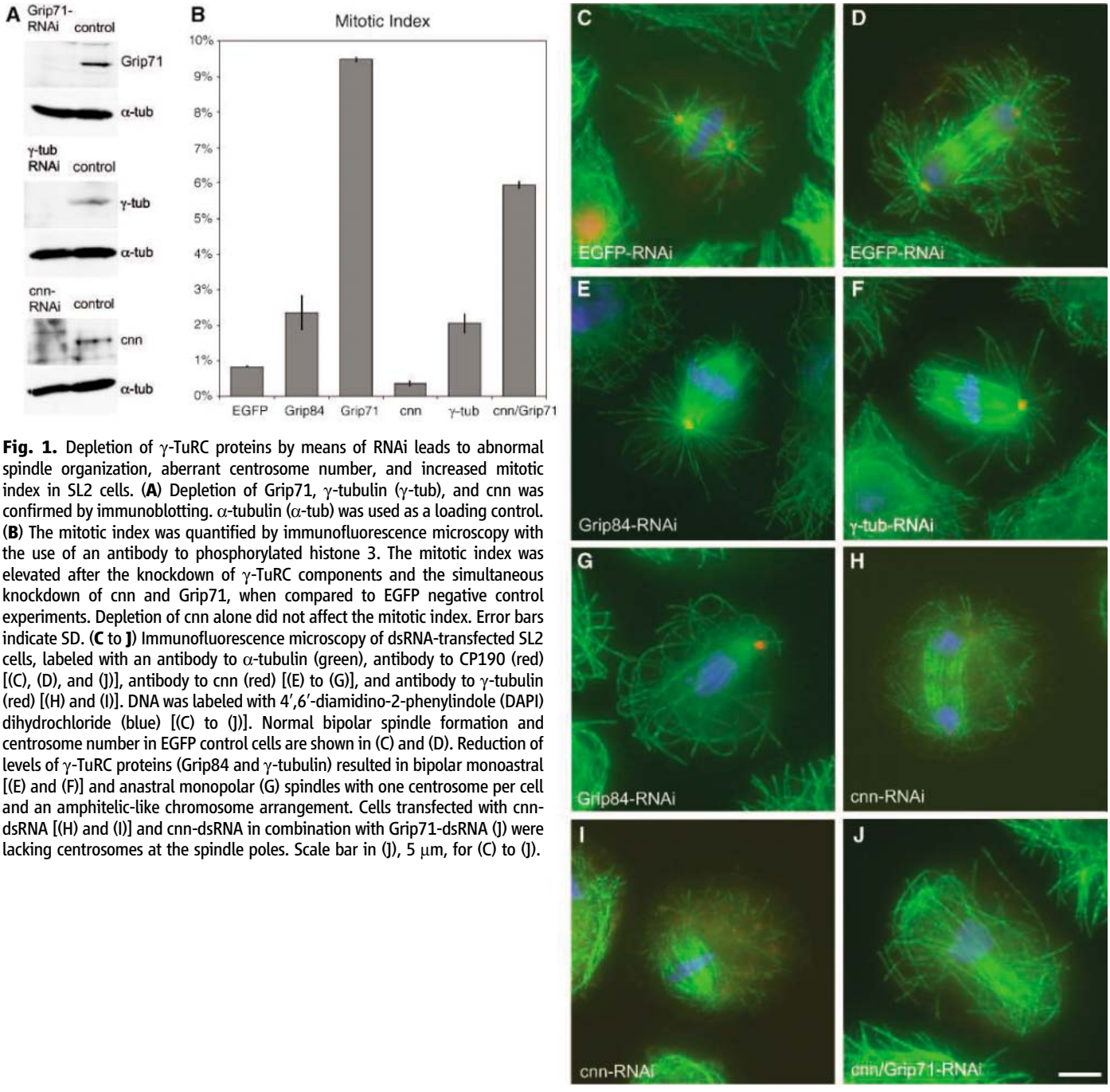

Fig. 1. Depletion of γ-TuRC proteins by means of RNAi leads to abnormal spindle organization, aberrant centrosome number, and increased mitotic index in SL2 cells. (**A**) Depletion of Grip71, γ-tubulin (γ-tub), and cnn was confirmed by immunoblotting. α-tubulin (α-tub) was used as a loading control. (**B**) The mitotic index was quantified by immunofluorescence microscopy with the use of an antibody to phosphorylated histone 3. The mitotic index was elevated after the knockdown of γ-TuRC components and the simultaneous knockdown of cnn and Grip71, when compared to EGFP negative control experiments. Depletion of cnn alone did not affect the mitotic index. Error bars indicate SD. (**C** to **J**) Immunofluorescence microscopy of dsRNA-transfected SL2 cells, labeled with an antibody to α-tubulin (green), antibody to CP190 (red) [(C), (D), and (J)], antibody to cnn (red) [(E) to (G)], and antibody to γ-tubulin (red) [(H) and (I)]. DNA was labeled with 4′,6′-diamidino-2-phenylindole (DAPI) dihydrochloride (blue) [(C) to (J)]. Normal bipolar spindle formation and centrosome number in EGFP control cells are shown in (C) and (D). Reduction of levels of γ-TuRC proteins (Grip84 and γ-tubulin) resulted in bipolar monoastral [(E) and (F)] and anastral monopolar (G) spindles with one centrosome per cell and an amphitelic-like chromosome arrangement. Cells transfected with cnn-dsRNA [(H) and (I)] and cnn-dsRNA in combination with Grip71-dsRNA (J) were lacking centrosomes at the spindle poles. Scale bar in (J), 5 μm, for (C) to (J).

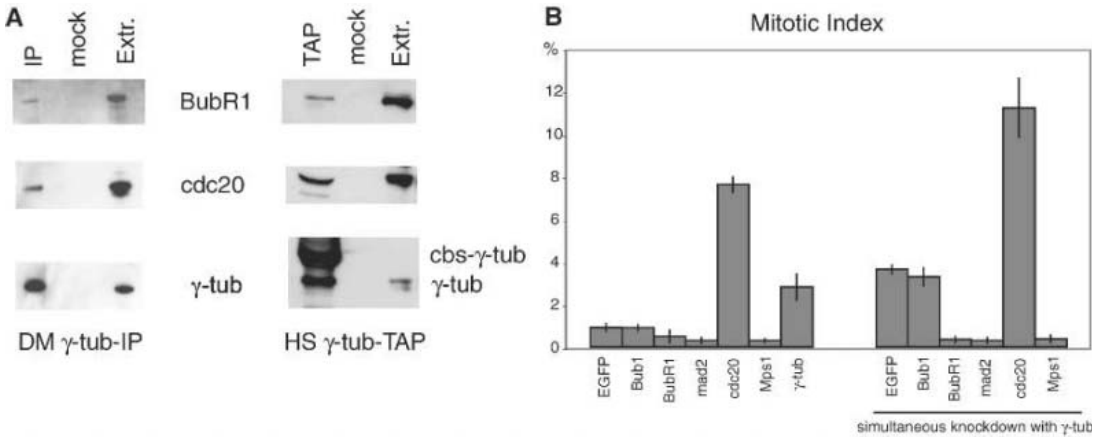

Fig. 2. (**A**) Coimmunoprecipitation experiments show that γ-tubulin, Cdc20, and BubR1 were in a complex. Immunoblotting analyses of immunopurified (IP) γ-tubulin from *Drosophila* (DM) embryonic extract (left panel) and tandem affinity purified (TAP) γ-tubulin from human (HS) cell extract (right panel) are shown. γ-tubulin was purified as detected with the antibody to γ-tubulin in both experiments. In the TAP experiments, the endogenous γ-tubulin as well as the larger γ-tubulin fusion protein with the calmodulin-binding site (cbs-γ-tub) were detected. BubR1 and Cdc20 were copurified with γ-tubulin. The mock purifications (mock) with the use of either nonimmune rabbit immunoglobins (left panel) or human immunoglobins and calmodulin beads (right panel) were negative. *Drosophila* embryonic or human cell extracts (Extr.) were used as positive controls for antibody labeling. (**B**) Depletion of γ-tubulin activates the spindle checkpoint, whereas the double knockdown confirms that γ-tubulin and Cdc20 functionally interact. The mitotic index of *Drosophila* SL2 cells was determined by immunofluorescence microcopy after single (left) or simultaneous (right) depletion experiments. Depletion of γ-tubulin and Cdc20 led to an increased mitotic index when compared to negative control cells. The simultaneous knockdown of Cdc20 with γ-tubulin resulted in an accumulative increase of mitotic cells. In contrast, the simultaneous depletion of checkpoint kinases (except Bub1) with γ-tubulin resulted in a reduced mitotic index in comparison to the EGFP/γ-tubulin control. Error bars indicate SD.

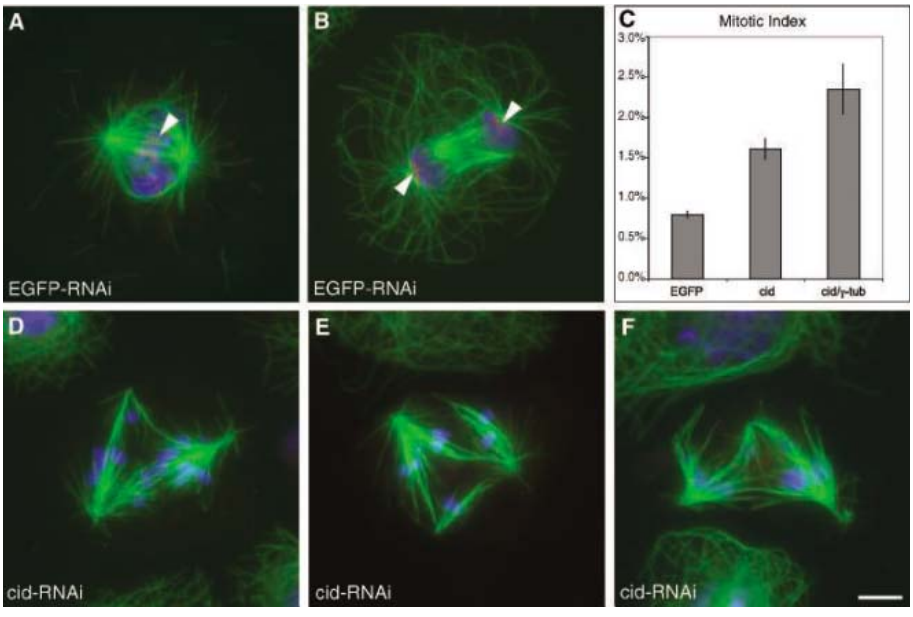

Fig. 3. RNAi of CID, an inner kinetochore protein, causes mitotic arrest and aberrant spindle formation and chromosome arrangements in *Drosophila* **SL2 cells.** (**A** and **B**) Labeling of control cells with antibodies to CID and α-tubulin detected a distinct kinetochore structure and normal microtubule organization during different mitotic stages. Arrowheads indicate CID labeling (red/yellow). DNA was labeled with DAPI (blue) (**C**) In comparison to control cells, depletion of CID by means of RNAi triggered a mitotic arrest that was increased further through double knockdown with γ-tubulin. Error bars indicate SD. (**D** to **F**) In immunofluorescence microscopy, CID was not detected after RNAi, demonstrating its efficient depletion from the kinetochore. The frequent metaphase arrest and displaced chromosomes indicated the microtubule-kinetochore attachment defect. Scale bar in (F), 5 μm, for (A), (B), and (D) to (F).

nents triggers mitotic arrest and impedes centrosome separation or duplication, whereas the removal of the centrosomal core protein cnn does not.

This discovery raised the questions of (i) how the depletion of γ-tubulin could activate arrest and whether this specific trigger (ii) requires an intact centrosome or (iii) is independent of centrosome localization. To address these questions, we depleted γ-TuRC proteins in the absence of an intact MTOC structure.

The simultaneous knockdown of cnn and Grip71 triggered mitotic arrest in the absence of a detectable centrosome (Fig. 1J). Thus, an intact centrosome is not a prerequisite for the γ-TuRC–mediated mitotic arrest. This result suggested at least two explanations: The depletion of microtubule nucleation factors will probably lead to a reduced number of microtubules. As a consequence, microtubule-kinetochore attachment is more likely to be absent and thus trigger the spindle checkpoint (*21*). Furthermore, γ-tubulin might be part of a signaling complex that actually activates the checkpoint when depleted.

Our hypothesis is that the reduction of microtubule density is not the sole trigger for mitotic arrest, because overall microtubule density was reduced in only a fraction of the arrested cells (Fig. 1G); most mitotically arrested cells in the γ-TuRC RNAi experiment showed abundant microtubule arrays with amphitelic-like chromosome microtubule attachment (Fig. 1, E and F). Thus, we tested whether the γ-TuRC components might be part of a signaling complex, triggering the spindle checkpoint when γ-TuRC proteins were abrogated. Checkpoint components are Cdc20, as part of the anaphase-promoting complex, regulating sister chromatid separation; and the kinases BubR1, Bub1, Mad2, and Mps1, which have been proposed to sense the occupancy or lack of tension at the microtubule plus ends (*22*).

We investigated the possible interaction of spindle assembly checkpoint components with γ-TuRC both on a functional and on a biochemical level, using RNAi, immunoprecipitation (IP), and tandem affinity purification (TAP) approaches (*17*). We purified γ-tubulin complexes by IP from *Drosophila* preblastoderm extracts and by TAP from mitotically synchronized human cells (fig. S1). Biochemical analysis of the complexes revealed that γ-tubulin was in a complex with BubR1 and Cdc20 in *Drosophila* and human cells (Fig. 2A), demonstrating an evo-

lutionarily conserved association of Cdc20 and BubR1 with γ-TuRC components. The molecular interaction data, from both *Drosophila* and human cells, suggested a mechanism coupling the spindle assembly checkpoint to γ-TuRC.

Because BubR1 and Cdc20 were in a complex with γ-tubulin, we investigated the functional importance of this interaction for the activation of the spindle checkpoint. A true spindle checkpoint protein is described as a component required for the activation of the checkpoint (*22*). In its absence, cells do not arrest in metaphase but separate sister chromatids and then exit mitosis (*23*, *24*). We used this property of the spindle checkpoint kinases to test whether depletion of γ-tubulin actually triggers a true spindle checkpoint or leads to an increase of the mitotic index through another pathway. The simultaneous knockdown of γ-tubulin and either of the checkpoint kinases described above had (apart from Bub1) a much-reduced mitotic index when compared to the EGFP/γ-tubulin control knockdown (Fig. 2B). This means that these checkpoint proteins were necessary for the γ-tubulin depletion–mediated mitotic arrest, confirming that γ-tubulin triggered a proper spindle assembly checkpoint response. As expected, Bub1 did not show any significant difference in the mitotic rate when compared to the negative control EGFP/γ-tubulin knockdown (Fig. 2B) (*25*). In addition, the simultaneous knockdown between Cdc20 and γ-tubulin increased the percentage of mitotic cells when compared to the Cdc20 single knockdown (Fig. 2B). Thus, the effects of γ-tubulin and Cdc20 depletion are cumulative, and γ-tubulin and Cdc20 interact functionally, which agrees with our biochemical data that γ-tubulin and Cdc20 are in a complex.

The kinetochore is composed of transiently associated proteins such as the checkpoint proteins, as well as more structural proteins [for example, CENP-B, CENP-C, and the histone H3–related protein CENP-A (CID in *Drosophila*)] (*26*). To test the respective contribution of signaling to the checkpoint from γ-TuRC and from the kinetochore, we removed a structural component of the kinetochore in SL2 cells. We achieved this step by using RNAi of the *Drosophila* CENP-A homolog CID (Fig. 3), a protein that is localized in or close to the inner plate of the *Drosophila* kinetochore and is required for kinetochore assembly (*27*). The efficient depletion of CID (Fig. 3, D to F) as compared to control cells (Fig. 3, A and B) caused mitotic arrest (Fig. 3C) and displaced the chromosomes from the metaphase plate (Fig. 3, D to F), suggesting microtubule-kinetochore attachment defects. Knockdown of γ-tubulin together with CID caused a further increase in the mitotic index when compared to single CID knockdown (Fig. 3C). This supports our hypothesis that γ-TuRC depletion is likely to activate an additional spindle checkpoint signal.

It has been suggested that the centrosome serves as a complex platform for multiple cellular signaling pathways (*2*, *3*, *28*). For example, cyclin B degradation, catalyzed through Cdc20, starts on the centrosome, thus functioning as a molecular hub integrating the interaction of proteins that regulate mitotic progression (*28–30*). Here we provide evidence that γ-TuRC proteins, rather than the centrosome per se, play a molecular role in the activation of the spindle checkpoint. We propose that γ-TuRC proteins are integrated in a signaling mechanism at the microtubule minus ends, and they are interacting with spindle checkpoint components independently of centrosome integrity.

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31. We acknowledge R. Aebersold, I. A. Dawson, G. Goshima, A. C. Gringas, G. Karpen, T. Kaufman, C. Sunkel, R. Vale, W. Whitfield, and Y. Zheng for the gift of antibodies, cells, and DNA constructs; the help of S. Haesler and D. Weichart with parts of the fluorescence-activated cell sorting and IP experiments; and our colleagues and A. Ploubidou for their comments on the manuscript. The work in the laboratory of B.M.H.L. is funded through the Berliner Senat für Kultur, Wissenschaft und Forschung, Project Ultrastructural Network, European Funds for Regional Development; by the Bundesministerium fur Bildung und Forschung, German Network for Genome Research 2, Systematic-Methodological Platform–Protein; by the European Union; and by the Max-Planck Society and the Thyssen Foundation.

Supporting Online Material

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21 July 2006; accepted 18 September 2006
10.1126/science.1132834

Odorant Receptor–Derived cAMP Signals Direct Axonal Targeting

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In mammals, odorant receptors (ORs) direct the axons of olfactory sensory neurons (OSNs) toward targets in the olfactory bulb. We show that cyclic adenosine monophosphate (cAMP) signals that regulate the expression of axon guidance molecules are essential for the OR-instructed axonal projection. Genetic manipulations of ORs, stimulatory G protein, cAMP-dependent protein kinase, and cAMP response element–binding protein shifted the axonal projection sites along the anterior-posterior axis in the olfactory bulb. Thus, it is the OR-derived cAMP signals, rather than direct action of OR molecules, that determine the target destinations of OSNs.

Each olfactory sensory neuron (OSN) in the mouse expresses only one functional odorant receptor (OR) gene out of ~1000 members (*1–3*). Axons from OSNs expressing a given OR converge onto a specific site, the glomerulus, in the olfactory bulb (*4–6*). It has been proposed that OR molecules at axon termini may directly recognize guidance cues on the olfactory bulb and mediate homophilic interactions of like axons (*6–10*). OR molecules are heterotrimeric guanine nucleotide–binding protein (G protein)–coupled receptors (GPCRs) that transduce the odorant-binding signals by activating the olfactory-specific G protein (G_{olf}) expressed in mature OSNs. The activation of G_{olf} stimulates adenylyl cyclase type III, generating cAMP, which opens cyclic nucleotide–gated (CNG) channels. Mice deficient for G_{olf} and CNGA2 are anosmic but form a normal glomerular map (*11–13*), which suggests that a

G protein other than G_{olf} may aid in targeting OSNs independent of CNG channels.

OR molecules are rhodopsin-like type A GPCRs that contain a conserved tripeptide motif, Asp-Arg-Tyr (DRY), at the cytoplasmic end of transmembrane domain III (fig. S1A), which is required for coupling of GPCRs to the partner G proteins (*14*, *15*). To examine whether the G protein signaling is involved in guidance of OSN axons, we generated a DRY-motif mutant, Arg-Asp-Tyr (RDY), for the rat OR gene *I7* (*16*) and expressed it using a transgenic system (*17*) (fig. S1B). Axons from OSNs expressing the wild-type I7, I7(WT), converged to a specific site in the olfactory bulb (Fig. 1A, left), whereas those expressing the DRY-motif mutant, I7(RDY), remained in the anterior region of the olfactory bulb, failing to converge onto a specific glomerulus (Fig. 1A, right). The I7(RDY)-expressing axons never penetrated the glomerular layer but stayed within the olfactory nerve layer (Fig. 1B). These axon termini were devoid of synaptotagmin (presynaptic marker) and microtubule-associated protein 2 (dendritic marker) immunoreactivities and thus probably did not form synapses (Fig. 2A, middle, and fig. S2). OSNs expressing a nonfunctional OR gene can activate other OR genes and will fail to converge onto a single glomerulus (*8*, *18*, *19*). However, the inability of I7(RDY) axons to converge on a specific glomerulus was not due to the coexpression of other OR genes (fig. S3); OSNs expressing the I7(RDY) transgene expressed no other OR genes. OSNs expressing I7(WT) all showed Ca^{2+} signals in response to octanal (an agonist of the I7 receptor), whereas those expressing I7(RDY) did not (Fig. 1C). Thus, the I7(RDY) mutant is deficient in both axon targeting and G protein coupling.

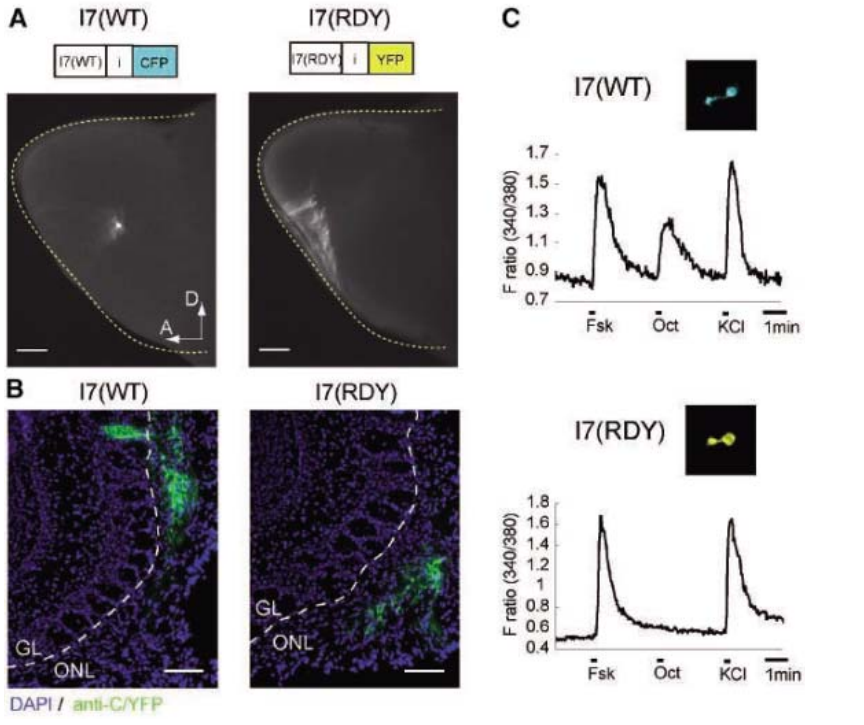

Fig. 1. A DRY-motif mutant of I7 OR. The DRY sequence in the wild-type OR, I7(WT), was changed to RDY in the mutant protein, I7(RDY). (**A**) Whole-mount fluorescent views of olfactory bulbs at postnatal day 14 (P14). Medial aspects are shown. Dotted yellow lines demarcate olfactory bulbs. A, anterior; D, dorsal; i, IRES. Scale bars, 500 μm. (**B**) Coronal sections of olfactory bulbs, stained with antibodies to C/YFP (green) and 4′,6′-diamidino-2-phenylindole (DAPI) (blue). Dashed lines demarcate the olfactory nerve layers (ONL) from the glomerular layers (GL). Scale bars, 100 μm. (**C**) Fura-2 calcium imaging. OSNs responsive to forskolin (an activator of adenylyl cyclase) were analyzed. Cells expressing the I7(WT) all responded to octanal (n = 12 OSNs), whereas those expressing I7(RDY) did not (n = 10). Fsk, 50 μM forskolin; Oct, 500 μM octanal. F ratio (340/380), the ratio of fura-2 fluorescence intensities at 510 nm with excitation at 340/380 nm. Insets show the C/YFP fluorescent images of OSNs analyzed.

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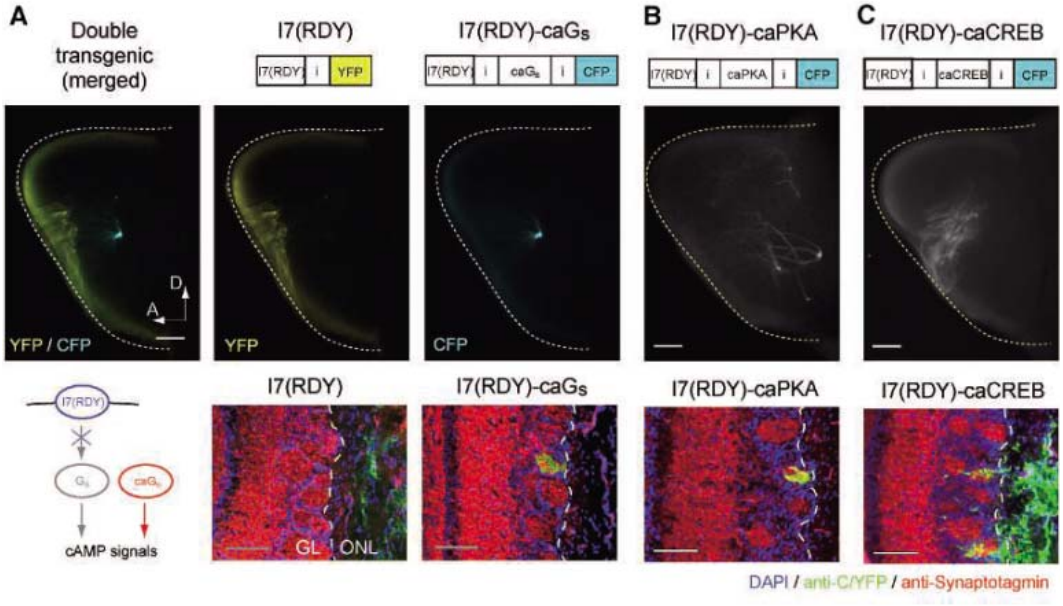
Fig. 2. Rescue of the I7(RDY) phenotype in OSN projection. (**A**) I7(RDY)-caG$_s$. (**B**) I7(RDY)-caPKA. (**C**) I7(RDY)-caCREB. Whole-mount fluorescent views are shown for the medial surface of the olfactory bulbs (age P14). The source of cAMP signals is schematically shown in (A) for I7(RDY)-caG$_s$. Coronal sections stained with antibodies to C/YFP (green) and DAPI (blue) are shown below. Synapse formation was examined with antibodies to synaptotagmin (red). Scale bars, 500 μm for the whole-mount bulbs, 100 μm for sections.



Both G_o and G_s genes are expressed in immature mouse OSNs (*20*). Although the G_s knockout mutation is embryonically lethal (*21*), the G_o-deficient mouse shows no obvious anatomical defect in the olfactory system (*22*). Because the DRY-motif mutant was assumed to be incapable of coupling with G proteins, we examined whether the constitutively active G_s (caG_s) mutant would rescue the defective phenotype of I7(RDY) in axonal projection. We inserted the caG_s gene into the I7(RDY) construct with an internal ribosome entry site (IRES), generating I7(RDY)-caG_s (fig. S1B). In OSNs expressing this construct, cAMP signals should be generated constitutively by caG_s in a receptor-independent manner. Axons expressing I7(RDY)-caG_s (Fig. 2A, cyan) converged to a specific site in the olfactory bulb, whereas axons expressing I7(RDY) (Fig. 2A, yellow) did not. Yellow fluorescent protein (YFP)–positive and cyan fluorescent protein (CFP)–positive axons did not intermingle or co-converge, which suggests that homophilic interaction of OR molecules is unlikely. Axons expressing I7(RDY)-caG_s were found within a glomerular structure and were immunoreactive for synaptotagmin (Fig. 2A, right). G_s stimulates adenylyl cyclase to produce cAMP, which in turn activates cAMP-dependent protein kinase (PKA). A constitutively active PKA rescued the defective phenotype of I7(RDY) in OSN projection and glomerular formation, although a few projection sites were found in the posterior region in the olfactory bulb (Fig. 2B). When the I7(RDY) construct was coexpressed with a constitutively active variant of cAMP response element–binding protein (CREB), a PKA-regulated transcription factor, axon termini were found within glomerular structures, although with incomplete convergence (Fig. 2C). These results confirm the role of G proteins in OSN axon targeting and suggest the involvement of cAMP in transcriptional regulation of axon guidance molecules.

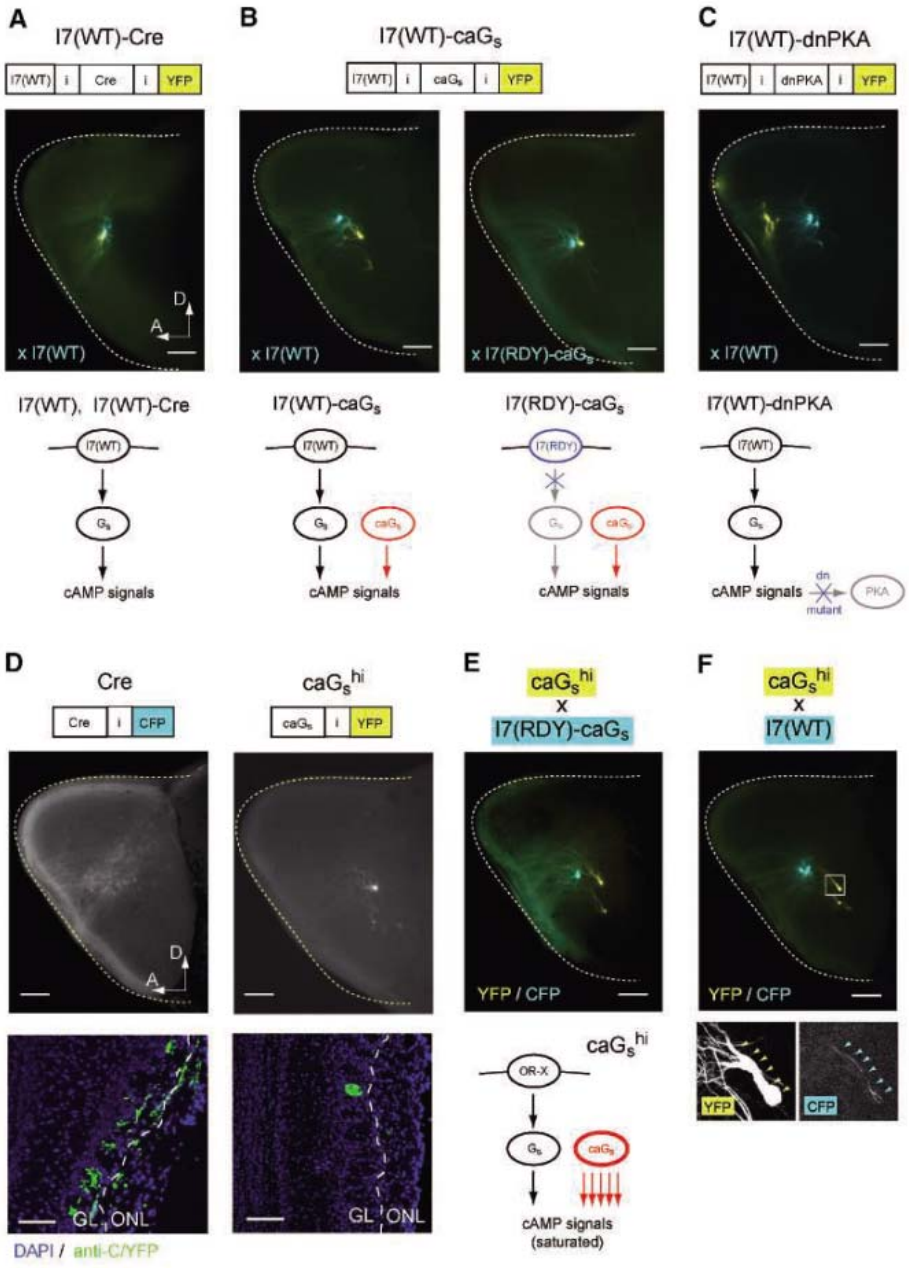


Fig. 3. Genetic manipulations of cAMP signals. Whole-mount fluorescent views of olfactory bulbs (medial surface) were analyzed for various double transgenic mice (age P14). OSN axons expressing the transgenes were visualized with CFP (cyan) or YFP (yellow). (**A**) YFP-tagged I7(WT)-Cre / CFP-tagged I7(WT). (**B**) Left, YFP-tagged I7(WT)-caG_s / CFP-tagged I7(WT); right, YFP-tagged I7(WT)-caG_s / CFP-tagged I7(RDY)-caG_s. (**C**) YFP-tagged I7(WT)-dnPKA / CFP-tagged I7(WT). (**D**) Coding region–replaced transgenic constructs, Cre and caG_s^{hi}. (**E**) CFP-tagged I7(RDY)-caG_s / YFP-tagged caG_s^{hi}. (**F**) YFP-tagged caG_s^{hi} / CFP-tagged I7(WT). Higher power confocal views of the boxed area (insets) are also shown. Arrowheads indicate the trajectories of labeled axons. Sources of cAMP signals are schematically shown for the OSNs expressing the respective transgenic constructs. Scale bars, 500 μm for whole-mount bulbs, 100 μm for sections.

To study cAMP signaling in OSN projection, we examined the effect of caG_s on OSNs expressing the wild-type OR. Two transgenic constructs, I7(WT)-Cre and I7(WT)-caG_s, were analyzed. The *Cre* recombinase gene was assumed not to affect the G_s-mediated signaling. Axons from OSNs expressing I7(WT)-Cre (Fig. 3A, yellow) or I7(WT) (Fig. 3A, cyan) converged in similar regions, whereas those expressing I7(WT)-caG_s (Fig. 3B, left) projected to more posterior regions. Additional cAMP signals are generated by caG_s. In OSNs expressing I7(WT)-caG_s, cAMP signals are generated by both the transgenic caG_s and endogenous G_s, whereas, in OSNs expressing I7(RDY)-caG_s, the generation of cAMP signals by endogenous G_s is blocked. The glomerulus for I7(WT)-caG_s (Fig. 3B, yellow) showed a smaller posterior shift from that for I7(RDY)-caG_s (Fig. 3B, cyan). Thus, the signaling level of the endogenous G_s appears to be relatively low when coupled with the wild-type OR. We also tested whether decreased levels of cAMP signals would affect the OSN projection. Axons expressing a dominant-negative PKA (dnPKA) with the wild-type OR converged to the anterior part of the olfactory bulb (Fig. 3C). Unlike axons carrying I7(RDY), axons expressing the I7(WT)-dnPKA construct generated glomerular structures. These transgenic experiments indicate that increased or decreased levels of cAMP signals shift the glomerular target of OSNs posteriorly or anteriorly, respectively.

To examine the effect of excessive cAMP signals on OSN projection, we generated the transgenic construct, caG_s^{hi}, in which the OR coding sequence has been replaced with the caG_s gene (fig. S1B). More caG_s was translated from the cap-dependent caG_s^{hi} than from the IRES-mediated I7(RDY)-caG_s (*8*). Although we

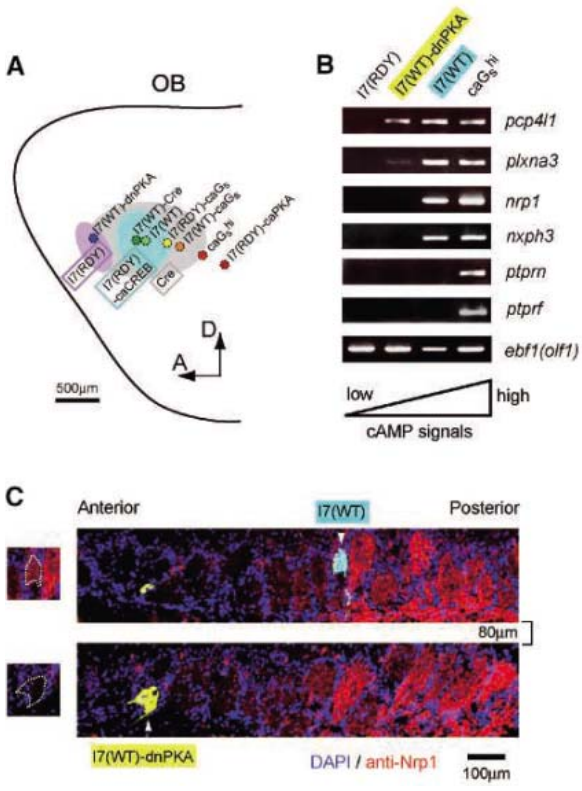


Fig. 4. Glomerular locations and cAMP signal levels. (**A**) Projection sites on the medial surface of the olfactory bulb (OB) are schematically shown for various transgenic constructs (fig. S6B). (**B**) RT-PCR analyses of single OSNs. cDNA libraries were prepared from single OSNs of four different transgenic mice: I7(RDY), I7(WT)-dnPKA, I7(WT), and caG$_s^{hi}$. The genes up-regulated by the cAMP signals were screened with microarray and RT-PCR analyses. Mixtures of 20 single-cell cDNA samples were analyzed by RT-PCR for the expression of isolated genes. Six examples are shown: *pcp4l1*, *plxna3*, *nrp1*, *nxph3*, *ptprn*, and *ptprf*. The gene *ebf1* (*olf-1*) was used as a control. (**C**) Expression profiles of Nrp1 in the olfactory bulb. Two horizontal olfactory bulb sections (80 μm apart) from the I7(WT)/I7(WT)-dnPKA double transgenic mouse (age P14) were immunostained with antibodies to Nrp1 (red). The posteriorly located I7(WT) glomerulus (cyan, arrowhead) was immunoreactive for Nrp1, whereas the anteriorly located I7(WT)-dnPKA glomerulus (yellow, arrowhead) was not. On the left, the I7(WT) and I7(WT)-dnPKA glomeruli (dotted traces) are compared for the Nrp1 expression. Quantitative analyses of glomeruli for Nrp1 expression are shown in fig. S5.

expected a posteriorly shifted but scattered pattern of projection with caG$_s^{hi}$, we detected only one or a few glomeruli (Fig. 3D). Projection sites driven by caG$_s^{hi}$ were located posterior to the I7(RDY)-caG$_s$ glomeruli (Fig. 3E). In situ hybridization and single-cell reverse transcription polymerase chain reaction (RT-PCR) indicate that OSNs expressing caG$_s^{hi}$ express multiple OR species (fig. S3). In the double transgenic mouse carrying CFP-tagged I7(WT) and YFP-tagged caG$_s^{hi}$, a few I7(WT)-expressing axons that probably also expressed caG$_s^{hi}$ projected to the caG$_s^{hi}$ glomerulus (Fig. 3F). Thus, the caG$_s^{hi}$ glomerulus represents a heterogeneous population of axons expressing different ORs. It is possible that caG$_s^{hi}$ produces saturated levels of cAMP signals and generates a distinct glomerular structure regardless of the OR species.

In contrast to G$_{olf}$, G$_s$ is expressed early in OSN differentiation (*11*). Our experiments suggest the involvement of a PKA-regulated transcription factor, CREB, in OSN projection (Fig. 2C). We used microarray and RT-PCR analyses to screen for genes with expression levels correlated with cAMP signals. cDNA libraries were prepared from single OSNs from four different transgenic mice, and gene expression profiles were compared between caG$_s^{hi}$ and I7(RDY) and between I7(WT) and I7(WT)-dnPKA (Fig. 4, A and B). Among the genes differentially expressed were some encoding axon guidance molecules [for example, neuropilin-1 (Nrp1)]. *Nrp1* was expressed in the caG$_s^{hi}$ OSNs (where cAMP signals might be high), but not in the I7(RDY)-expressing OSNs (where cAMP signaling is blocked) (Fig. 4B and fig. S4). Immunostaining demonstrated a gradient of Nrp1 expression, with low expression in the anterior and high expression in the posterior of the olfactory bulb (fig. S5). In the I7(WT) / I7(WT)-dnPKA mouse, the I7(WT) glomerulus (Fig. 4C, cyan, posterior) was Nrp1-positive, and the I7(WT)-dnPKA glomerulus (Fig. 4C, yellow, anterior) was Nrp1-negative. Nrp1 has been implicated in guidance of OSN axons, because the disruption of the *Sema3A* gene, which encodes a repulsive ligand for Nrp1, alters glomerular arrangements along the anterior-posterior axis (*23*, *24*). We suggest that G$_s$-mediated cAMP signals regulate the transcription of genes encoding axon guidance molecules, which in turn guide positioning of glomeruli.

Our results explain some puzzling observations about OSN targeting. The β$_2$-adrenergic receptor (β$_2$AR), but not a vomeronasal receptor (V1rb2), can substitute for an OR in OR-instructed axonal outgrowth and glomerular formation (*8*). The explanation for this observation may be that the β$_2$AR can couple to G$_s$, but the V1rb2 cannot. This explanation is consistent with the idea that the G$_s$-mediated cAMP levels set by the receptors determine the target sites of OSN axons. Another puzzling observation is that alterations in OR expression levels can affect OSN projection (*8*). The level of cAMP signals may be affected by both OR identity and the amount of OR protein, which would be a factor of transcription and translation parameters. OR-instructed G$_s$ signals are not dependent on odorants (*23*), and disruption of G_{olf} or *CNGA2* genes did not affect positioning of glomeruli (*11*–*13*), which suggests that G$_s$-mediated cAMP signaling is distinct from that mediated by odor-evoked neuronal activity. It has been thought that ORs at axon termini may recognize guidance cues on the olfactory bulb and mediate the homophilic interactions of like axons (*6*–*10*). However, our results favor a model in which cAMP signals regulate the targeting of OSN axons along the anterior-posterior axis (fig. S6A). These results complement previous studies indicating that the dorsal-ventral arrangement of glomeruli is determined by the locations of OSNs within the olfactory epithelium (*25*–*27*). We propose that a combination of dorsal-ventral patterning, based on anatomical locations of OSNs, and anterior-posterior patterning, based on OR-derived cAMP signals, establishes olfactory bulb topography. After OSN axons reach their approximate destinations in the olfactory bulb, further refinement of the glomerular map may occur through fasciculation and segregation of axon termini in an activity-dependent manner.

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Supporting Online Material
www.sciencemag.org/cgi/content/full/1131794/DC1
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27 June 2006; accepted 8 September 2006
Published online 21 September 2006;
10.1126/science.1131794
Include this information when citing this paper.

Molecular Phylogeny and Evolution of Morphology in the Social Amoebas

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The social amoebas (Dictyostelia) display conditional multicellularity in a wide variety of forms. Despite widespread interest in *Dictyostelium discoideum* as a model system, almost no molecular data exist from the rest of the group. We constructed the first molecular phylogeny of the Dictyostelia with parallel small subunit ribosomal RNA and α-tubulin data sets, and we found that dictyostelid taxonomy requires complete revision. A mapping of characters onto the phylogeny shows that the dominant trend in dictyostelid evolution is increased size and cell type specialization of fruiting structures, with some complex morphologies evolving several times independently. Thus, the latter may be controlled by only a few genes, making their underlying mechanisms relatively easy to unravel.

Multicellular animals and plants display an enormous variety of forms, but their underlying genetic diversity is small compared with the genetic diversity of microbes. Eukaryotic microbes include a broad range of unicellular life forms, with multiple independent inventions of multicellularity. One of the most intriguing challenges in biology is to understand the reason behind the repeated occurrence of this particular evolutionary stratagem.

The social amoebas, or Dictyostelia, are a group of organisms that hover on the borderline between uni- and multicellularity. Each organism starts its life as a unicellular amoeba, but they aggregate to form a multicellular fruiting body when starved. This process has been best described for the model organism *Dictyostelium discoideum*. The aggregate of up to 100,000 *D. discoideum* cells first transforms into a finger-shaped structure, the "slug." The head region of the slug senses environmental stimuli such as temperature and light and directs the slug toward the soil's outer surface, where spores will be readily dispersed. The slug then stands up to form the fruiting body, or sorocarp. The cells in the head region move into a prefabricated cellulose tube and differentiate into stalk cells that ultimately die. The remaining "body" cells then crawl up the stalk and encapsulate to form spores. Thus, the Dictyostelia display distinct characteristics of true multicellularity, such as cell-cell signaling, cellular specialization, coherent cell movement, programmed cell death, and altruism (*1*, *2*).

Traditionally, social amoebas have been classified according to their most notable trait, fruiting body morphology. Based on this, three genera have been proposed: *Dictyostelium*, with unbranched or laterally branched fruiting bodies; *Polysphondylium,* whose fruiting bodies consist of repetitive whorls of regularly spaced side branches; and *Acytostelium*, which, unlike the other genera, forms acellular fruiting body stalks (*1*).

Despite the widespread use of *D. discoideum* as a model organism (*2*, *3*), the Dictyostelia as a whole are poorly characterized in molecular terms; nearly all currently available data are from a single species. Nonetheless, the social amoebas provide a unique opportunity to understand the evolution of multicellularity (*4*–*6*). A primary and essential prerequisite for this is an understanding of the true phylogeny of the group. Here, we describe the phylogeny of social amoeba species and trace the acquisition of morphological and functional complexity during their evolution.

Nearly complete small subunit rRNA (SSU rDNA) gene sequences were determined from more than 100 isolates of Dictyostelia, including nearly every described species currently in culture worldwide (*7*). Phylogenetic analyses of these data identified four major subdivisions of the group, which we numbered 1 to 4 (Fig. 1 and fig. S1). Group 1 consists of a morphologically diverse set of *Dictyostelium* species. Group 2 is a mixture of species with representatives of all three traditional genera, including all pale-colored species of *Polysphondylium*, at least two species of *Dictyostelium*, and all species of *Acytostelium*. Group 3 is again a diverse set of purely *Dictyostelium* species, also including the single cannibalistic species, *D. caveatum*. The largest group is group 4, which consists almost entirely of *Dictyostelium* species but may also include a clade of two violet-colored species from two separate traditional genera, *P. violaceum* and *D. laterosorum.* With the exception of the violet-colored species, group 4 is a fairly homogeneous set of large robust species, including the model organism *D. discoideum* and the cosmopolitan species, *D. mucoroides*, which appears to be polyphyletic (*8*).

The four SSU rDNA groupings are confirmed by α-tubulin phylogeny (fig. S2) with two exceptions: (i) *A. ellipticum* is only weakly placed with group 2 in the α-tubulin tree (fig. S2), and (ii) the *D. laterosorum* and *P. violaceum* clade is grouped together with *D. polycephalum* as the sister group to a weakly supported group 3 plus group 4 clade (0.64 Bayesian inference posterior probability, 51% maximum likelihood bootstrap, fig. S2). This is in contrast to its position as the exclusive sister lineage to group 4 in the SSU rDNA tree (Fig. 1). The SSU rDNA phylogeny also strongly supports group 1 as the deepest major divergence in Dictyostelia (Fig. 1 and fig. S1), as do analyses of combined SSU rDNA plus α-tubulin nucleotide sequences (fig. S3). However, an alternative root is weakly recovered in the α-tubulin amino acid phylogeny (fig. S2). Thus, the position of the dictyostelid root still requires confirmation, which will probably require multiple additional genes.

A notable feature of both phylogenies is the split of the genus *Polysphondylium*. The violet-colored *P. violaceum* is unequivocally grouped together with *D. laterosorum*, and these two lie together at the base of group 4 (Fig. 1) or in groups 3 and 4 (fig. S2). Meanwhile, the pale-colored polysphondylids are all found nested within group 2 (Fig. 1 and

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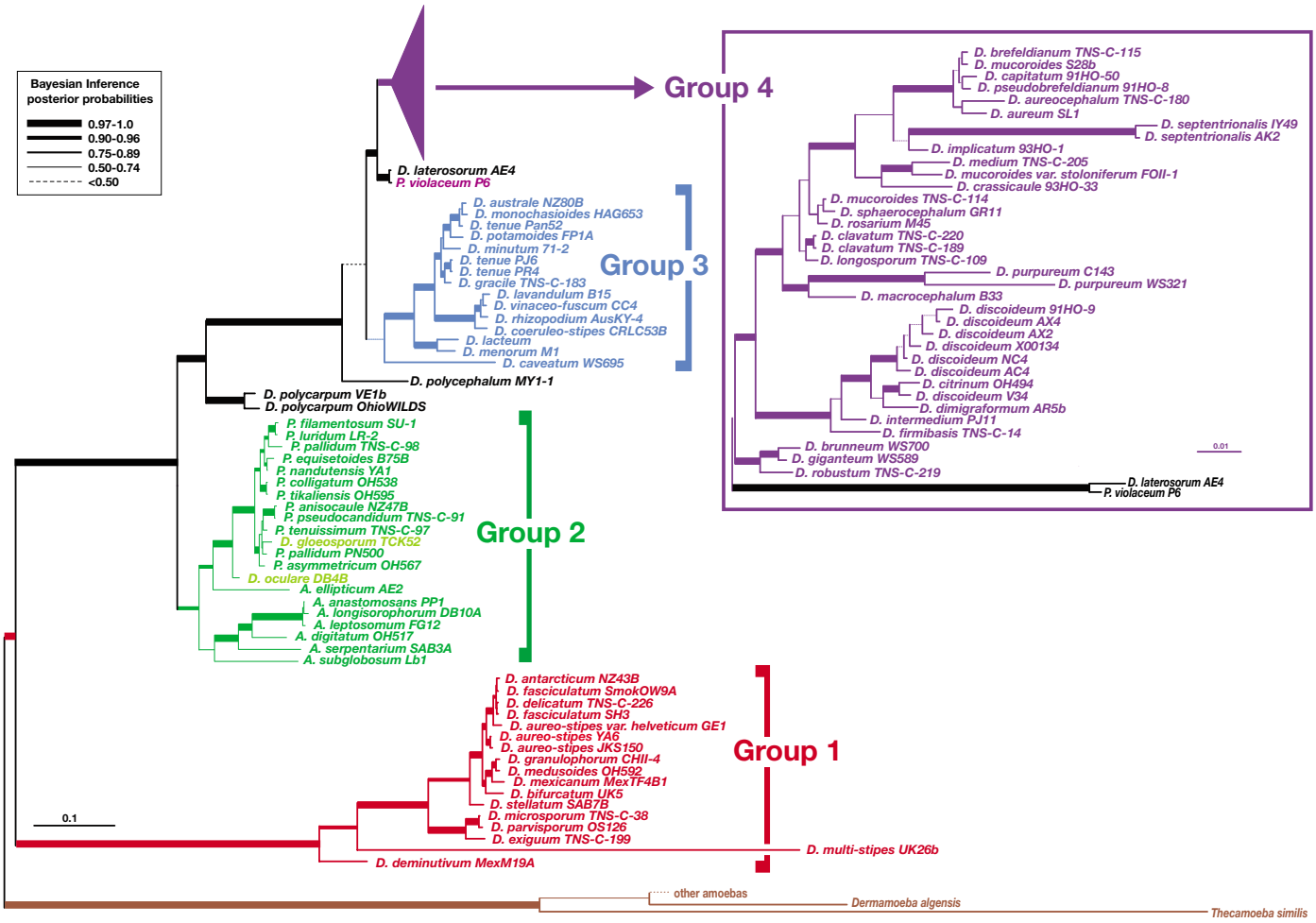

Fig. 1. A universal phylogeny of the Dictyostelia based on SSU rDNA sequences. The tree shown was derived by Bayesian inference from 1655 aligned positions (*7*). Four major taxonomic divisions were identified (groups 1 to 4), which are indicated by separate colors and to the right of the figure beside brackets (*Dictyostelium* species within group 2 are indicated in lighter green). The tree includes nearly all known and described species of *Dictyostelium* (*D.*), *Polysphondylium* (*P.*), and *Acytostelium* (*A.*). Bayesian inference posterior probabilities are roughly indicated by line width (key at the upper left); exact Bayesian inference posterior probability and maximum likelihood bootstrap values are given in fig. S1A. Separate analyses were conducted on the group 4 sequences (*7*), including an additional 300 nucleotide positions that were more highly divergent (inset box in the upper right) (fig. S1B). Branch lengths are drawn to scale (substitutions per site) as indicated by scale bars. The tree is rooted based on separate analyses (*7*), including closely related lobosan amoebas (fig. S1C) (*12*). Branch lengths for lobosan amoebas were scaled up to compensate for the smaller number of alignable sites, based on the length of the first two internal branches (fig. S1C).

fig. S2). The dictyostelid SSU rDNA phylogeny also shows tremendous molecular depth that is roughly equivalent to that of animals and considerably greater than that of fungi (fig. S4). This suggests that Dictyostelia is a deep and complex taxon, but the true extent of this depth requires confirmation from a broader sampling of their genomes.

Social amoeba species show marked differences in the size and branching patterns of their fruiting bodies and the presence or absence and shape of support structures. They may also vary in spore characteristics, cell aggregation patterns, slug migration characteristics, and presence or absence of alternative life cycles, such as the microcyst and sexual macrocyst (*1*). To understand how these traits might have evolved, we mapped all well-documented dictyostelid traits onto the molecular phylogeny (Fig. 2 and fig. S5).

Few of the traditionally noted morphological characters show any clear trend across the tree, although a number show interesting within-group trends. The most globally consistent character appears to be spore shape (Fig. 2, column 2). Spores can be either round (globose) or oblong, and in the latter case they often have granules at their poles. Groups 1 and 3 are characterized by oblong spores with tightly grouped (consolidated) granules. In group 2, the granules have become loosely grouped (unconsolidated), whereas polar granules are lost entirely in group 4. Group 1 is further characterized by markedly smaller spores than the other taxa (Fig. 2, column 1).

Fruiting body (sorocarp) morphology and size are the most commonly used taxonomic characters. A primary determinant of sorocarp size is the number of cells that can be collected into one aggregate. However, most of the sorocarp size and shape variation depends on the extent and manner of subsequent aggregate subdivision (Fig. 2, columns 3 to 7; fig. S5, columns 15 to 19) (*7*). These characteristics are controlled by so-called organizing centers, or "tips," the first of which appears as a small protrusion on top of a newly formed aggregate. Secondary tips may then appear during or just after aggregation, giving rise to a gregarious or clustered sorocarp habit, respectively. The rising cell masses can subdivide even further by new tips arising along their main axis, yielding lateral branches, or by groups of cells detaching themselves from the rear. The latter abstricted masses can differentiate directly into spores or form new tips, giving rise to whorls of irregular or evenly spaced branches. Species in groups 1 to 3 usually display a clustered or gregarious sorocarp habit, whereas group 4 species mainly form solitary fruiting bodies (Fig. 2, column 2).

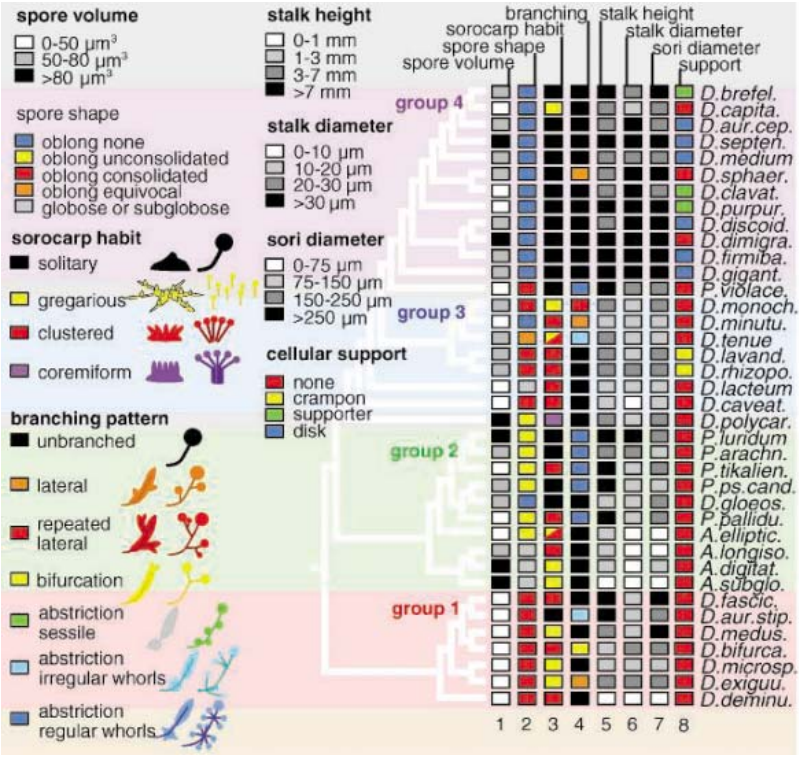

Fig. 2. Trait mapping of dictyostelid characters. Consistently documented characters were retrieved from primary species descriptions (table S1) and from *Dictyostelium* monographs (*1*, *11*). Character states were numerically coded and mapped to the dictyostelid SSU rDNA phylogeny, including alternate species (Fig. 1), with the MacClade 4 software package (*13*). For comprehensive presentation, the most informative characters are combinatorially presented on a single tree with the numerical code converted into color code for qualitative traits and into gray scale for quantitative traits. The code key for the character states is shown on the left side of the figure and in table S2. A total set of 20 characters mapped to all species in the phylogeny is presented in fig. S5.

Additionally, branched forms are much more common in groups 1 to 3 than in group 4. Not surprisingly, there is an inverse relationship between a tendency for aggregates and sorogens to subdivide and the size of stalk and sorus. Thus, group 4 species also have the largest sori and the thickest and longest stalks (Fig. 2, columns 5 to 7, and fig. S5). The presence of support structures formed from stalk-like cells such as basal disks, triangular supporters, or crampons also appear to be markedly correlated with large fruiting body size (Fig. 2, column 8).

Molecular phylogenetic analyses of two independent markers show that Dictyostelia consists of four major groups, none of which correspond to traditional classifications. The molecular tree is dominated by *Dictyostelium* species (which appear in all four groups), *Polysphondylium*s are found in two very separate locations, and *Acytostelium*s reside in a mixed group (group 2) that also includes *Dictyostelium* and *Polysphondylium* species. Therefore, none of the four molecularly defined dictyostelid groups correspond to traditional genera, and none of the traditional genera, with the possible exception of *Acytostelium*, are even monophyletic. This indicates that fruiting body morphology, upon which traditional classification is based, is a very plastic trait in Dictyostelia and is apparently of little use as a taxonomic determinant. This is even more evident from the scattered distribution of similar branching morphologies over the four taxon groups (fig. S5, columns 15 to 16). For instance, the rosary-type, coremiform, and laterally branched morphologies appear, respectively, two, three, and seven times independently across the tree.

The strongest evolutionary trend in dictyostelid fruiting body morphology appears to be related to size. Whereas the species in groups 1, 2, and 3 generally split up their aggregates into multiple sorogens, which then subdivide even further to yield branched fruiting bodies, the aggregates of group 4 species usually give rise to a solitary fruiting body that is only rarely branched. As a result, the group 4 species have more robust fruiting structures with much larger spore heads than the other groups. These large structures are typically supported at their base by basal disks or triangular supporters that are derived from a third cell type, the anterior-like cells. In at least one species, *D. discoideum*, this cell type diverges even further to produce two more structures, the upper and lower cup that support the spore head. This is an interesting example of the correlation between the size of an organism and its cell type diversity, which marks the evolution of many multicellular organisms (*9*).

The DNA-based phylogeny of the Dictyostelids indicates four high-level taxa, none of which correspond to the three traditional genera. Therefore, we sought unique descriptive names for each group. For group 1, we propose the name "Parvisporids" (parvi means small), because these species all have small spores. For group 2, we propose "Heterostelids," signifying their wide variety of fruiting body and stalk morphologies. We propose "Rhizostelids" for group 3, which includes species with rootlike support structures for their fruiting bodies. Finally, we propose that group 4 exclusively retain the name "Dictyostelid," because it includes the widely studied model organism *D. discoideum*.

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8. *D. mucoroides* appears in three separate clades in group 4. This is partly because the original holotype of Brefeld (*10*) was lost, and subsequent researchers made different diagnoses of more recent isolates. Hagiwara's *D. mucoroides* (strain number TNS-C-114) was diagnosed by Raper (*1*) as *D. sphaerocephalum*, whereas Raper's *D. mucoroides* (strain number S28b) was diagnosed as *D. brefeldianum* by Hagiwara (*11*).
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14. We thank honors research students L. Paternoster, S. Saleem, S. Wilkinson, and C. Williams for help with sequencing and early analyses and E. Vadell and J. C. Landolt for gifts of dictyostelid cultures. T.D. and T.W. thank R. Marschalek for SSU rDNA sequencing early in the project. This research was supported by Biotechnology and Biological Sciences Research Council (BBSRC) grants COD16760 and COD16761 to P.S. and S.L.B., BBSRC grant R01362 to S.L.B., Dutch Science Foundation (NWO) grant 805.17.047 to P.S., Wellcome Trust University Award Grant 057137 to P.S., and an NSF postdoctoral fellowship in Microbiology to D.E.R. Sequences reported in this paper have been deposited in the European Molecular Biology Laboratory (EMBL) database under accession numbers AM168028 to AM168115 (SSU rDNA) and AM168453 to AM168491 (α-tubulin).

Supporting Online Material

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31 May 2006; accepted 14 September 2006
10.1126/science.1130670

Control of Peripheral Nerve Myelination by the β-Secretase BACE1

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Although BACE1 (beta-site amyloid precursor protein–cleaving enzyme 1) is essential for the generation of amyloid-β peptide in Alzheimer's disease, its physiological function is unclear. We found that very high levels of BACE1 were expressed at time points when peripheral nerves become myelinated. Deficiency of BACE1 resulted in the accumulation of unprocessed neuregulin 1 (NRG1), an axonally expressed factor required for glial cell development and myelination. *BACE1*$^{-/-}$ mice displayed hypomyelination of peripheral nerves and aberrant axonal segregation of small-diameter afferent fibers, very similar to that seen in mice with mutations in type III NRG1 or Schwann cell–specific ErbB2 knockouts. Thus, BACE1 is required for myelination and correct bundling of axons by Schwann cells, probably through processing of type III NRG1.

The generation, aggregation, and deposition of amyloid-β peptide (Aβ) in the brains of Alzheimer's disease (AD) patients is an invariant pathological feature of this devastating neurodegenerative disease (*1*). Aβ is generated from the membrane-spanning β-amyloid precursor protein (APP) by endoproteolytic processing. Sequential cleavages, first by β-secretase and then by γ-secretase, are required to liberate Aβ into the extracellular space (*2*). β-Secretase activity is conferred by a type I transmembrane aspartyl protease, BACE1 (*3*–*7*). Other substrates for BACE1 include the sialyltransferase ST6Gal I (*8*, *9*), the adhesion protein P-selectin glycoprotein ligand-1 (PSGL-1) (*10*), β subunits of voltage-gated sodium channels (*11*), APP-like proteins (APLPs) (*12*), and Aβ itself (*13*–*15*). BACE1 is the sole β-secretase because no Aβ is synthesized in BACE1$^{-/-}$ mice (*16*–*19*). However, only modest behavioral alterations are seen after targeted mutation of *BACE1*, and its physiological function remains unclear (*19*, *20*).

Expression of BACE1 is confined mainly to neurons. Its activity could thus lead to release of substrates from neuronal membranes and thereby mediate paracrine signaling to neighboring cells, i.e., function in neuron-neuron or neuron-glia interactions. We investigated the expression of BACE1 in postnatal mice. The highest levels of BACE1 expression were observed in early postnatal stages, when myelination occurs (Fig. 1A). BACE1 expression declined in the second postnatal week, attaining low levels in adult animals (Fig. 1A). We hypothesized that the high expression of BACE1 in neurons around birth could be linked to the onset of myelination by Schwann cells, the ensheathing glia of peripheral nerves, which occurs at this time and which depends on signaling from the accompanying axons. In particular, the type III isoform of the epidermal growth factor (EGF)–like factor neuregulin 1 (NRG1), an axonal signal that activates heteromeric ErbB2 and ErbB3 receptors on Schwann cells, is important during Schwann cell development and myelination (*21*, *22*). Type III NRG1 adopts a two-transmembrane structure with the active EGF domain in the lumenal portion, which may require endoproteolysis for its signaling capacity (*23*). Haploinsufficiency of type III NRG1 or conditional knockout of ErbB signaling in Schwann cells leads to aberrant axonal ensheathment and hypomyelination in peripheral nerves, whereas overexpression of type III NRG1 results in hypermyelination (*24*–*26*). Owing to the tight temporal link between BACE1 expression and peripheral nerve myelination, we investigated whether BACE1 and type III NRG1 were coexpressed within sensory and motor neurons, whose axons project within peripheral nerves. In situ hybridization on spinal cord and dorsal root ganglia (DRG) from young postnatal mice revealed expression of BACE1 within the central

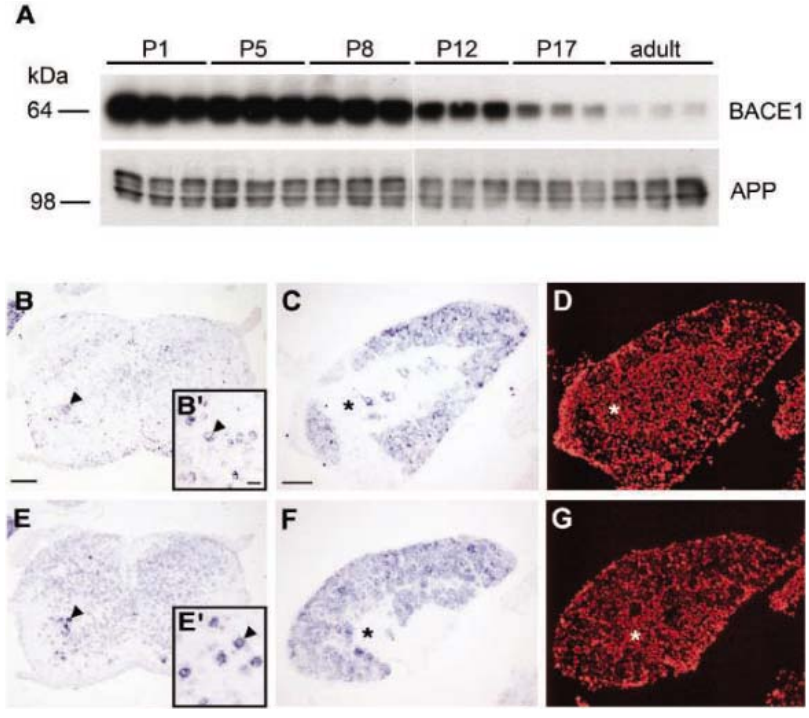

Fig. 1. BACE1 is highly expressed during the period of myelin formation and is coexpressed with type III NRG1 in neurons projecting to the periphery. (**A**) Immunoblot analysis of membrane preparations from CNS lysates of mice 1, 5, 8, 12, and 17 days old or of tissue from adults. BACE1 is highly expressed in the first postnatal week and is subsequently down-regulated. Levels of the BACE1 substrate, amyloid precursor protein (APP), remain relatively constant in postnatal animals of different ages. (**B** to **G**) Analysis of BACE1 expression (B to D) or type III NRG1 (E to G) at postnatal day 5 with digoxigenin-labeled riboprobes (B, C, E, and F). Both BACE1 and type III NRG1 are coexpressed in motor neurons (B, E, and higher-magnification insets B′ and E′; motor neurons are indicated by arrowheads) and peripheral sensory neurons in the DRG (C and F). Counterstaining with a nuclear marker [D and G; false-color DAPI (4′,6-diamidino-2-phenylindole) counterstain of the sections shown in C and F] shows an absence of BACE1 and type III NRG1 expression in Schwann cells and satellite glia (asterisks highlight glia in the nerve bundle within the DRG). Bars: (B and E), 200 μm; (B′ and E′), 40 μm; (C, D, F, and G), 100 μm.

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nervous system (CNS), notably in ventral horn motor neurons, as well as in peripheral sensory neurons in the DRG (Fig. 1, B to D). No expression of BACE1 could be detected in satellite glia of DRGs or Schwann cells (Fig. 1, C and D, asterisks). The pattern of BACE1 expression in spinal cord and DRGs was highly similar to that of type III NRG1 (Fig. 1, E to G), particularly in sensory and motor neurons.

Because defects in the extent of myelination are seen in mice with reduced signaling of type III NRG-1 (*25*, *26*), we studied the progression of myelination in the sciatic nerve of *BACE1*$^{-/-}$ mice using electron microscopy. Myelin sheath thickness, expressed as the G ratio [internal/external fiber diameter (*27*)], was determined in several hundred axons from pairs of mutants and controls at day 8, 12, and 17 of postnatal development and in adult animals. Axons of *BACE1*$^{-/-}$ mice were hypomyelinated at all stages (Fig. 2, A to F, and figs. S1 and S2; $P < 0.001$), whereas myelin ultrastructure was unchanged (Fig. 2, A and B, insets). Furthermore, individual large-diameter axons surrounded by single Schwann cells, which had failed to initiate myelination, were numerous in *BACE1*$^{-/-}$ mutants at postnatal day 8 (Fig. 2B, arrow). Hypomyelination was also observed in an independently generated BACE1 knockout (*17*) (fig. S3). We also examined the morphology of small-diameter axons, which are ensheathed and separated from each other by cytoplasmic processes of nonmyelinating Schwann cells to form Remak bundles. The bundling of such axons by nonmyelinating Schwann cells was significantly altered in *BACE1*$^{-/-}$ mice (Fig. 2, G to I) ($P < 0.001$), such that Remak bundles contained aberrantly large numbers of unseparated or poorly segregated axons.

β-Secretase activity in vitro can be demonstrated for both BACE1 and to a lesser extent for the homologous enzyme BACE2 (*28*–*31*). We thus analyzed the peripheral nerves of *BACE2* mutant mice, as well as *BACE1/BACE2* compound mutants, using the independently generated *BACE1* mutant for comparison (*17*, *32*) (fig. S3). Peripheral nerve myelination in *BACE2* mutant mice was unchanged, whereas *BACE1/BACE2* compound homozygotes displayed hypomyelination, very similar to that seen in *BACE1* homozygotes. Thus, regulation of nerve myelination by β-secretase activity is restricted to BACE1.

The changes observed in peripheral nerves of *BACE1*$^{-/-}$ mice phenocopied those previously observed in mice with haploinsufficiency of *NRG1* or in mice that lack ErbB signaling in Schwann cells, i.e., amyelination of a subset of large-diameter axons at early stages, hypomyelination into adulthood, and altered sorting of axons within Remak bundles by nonmyelinating Schwann cells (*24*–*26*). Because axonally expressed type III NRG1 determines the ensheathment fate of axons (*25*, *26*), we reasoned that the myelination phenotype in *BACE1*$^{-/-}$ mice might be due to an alteration in the BACE1-dependent presentation or availability of neuronal type III NRG1 to associated glia. Indeed, biochemical analysis of CNS membrane preparations revealed a robust accumulation of a 130-kD isoform of NRG1 in *BACE1*$^{-/-}$ mice (Fig. 3A), corresponding to the uncleaved type III precursor (*23*). The expression of NRG1 mRNA, in contrast, was unchanged in the brains of *BACE1*$^{-/-}$ mice (fig. S4). This is consistent with the accumulation of

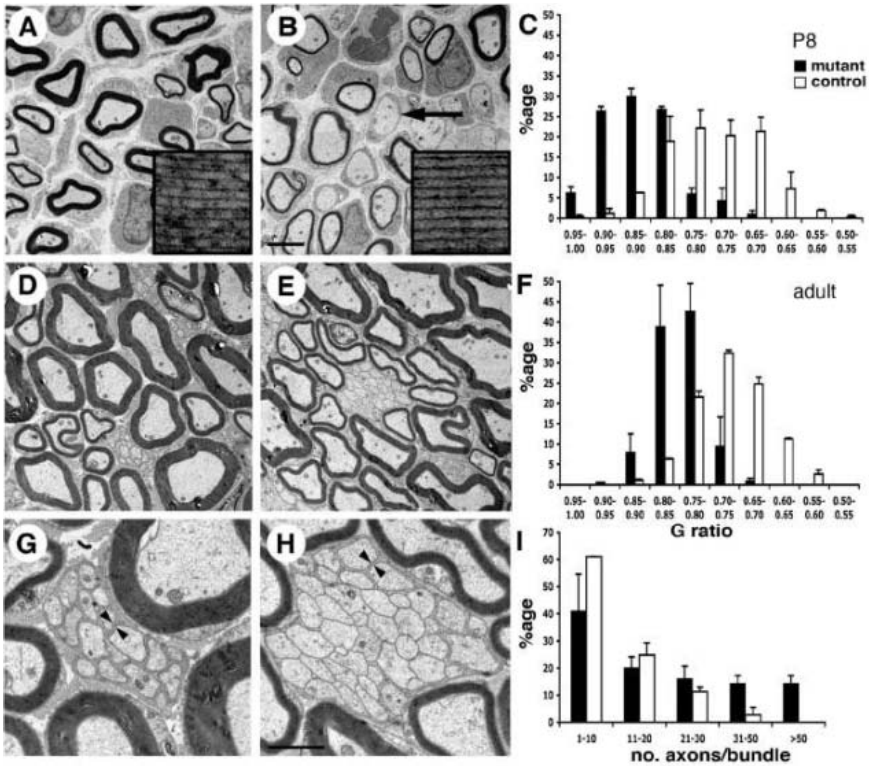

Fig. 2. *BACE1*$^{-/-}$ mice display hypomyelination of peripheral nerves and axonal-bundling abnormalities. Electron microscopy analysis of sciatic nerves of control (**A**, **D**, **G**) and *BACE1* mutant mice (**B**, **E**, **H**) in 8-day-old (A and B) and adult mice (D to H). G-ratio determinations at postnatal day 8 (**C**) and adult stages (**F**) are shown as the percentage of total myelinated axons. Insets (A and B) show normal ultrastructure of myelin lamellae in mutant mice. Amyelinated axons are abundant in *BACE1*$^{-/-}$ mice at postnatal day 8 (B, arrow). (**G** to **I**) Sorting of small-diameter axons by Schwann cell cytoplasmic processes within Remak bundles is defective in *BACE1* mutants. Arrowheads in (G) and (H) indicate cytoplasm between different axons, which isolates each individual axon within the Remak bundles of controls. *BACE1* mutants contain unusually large Remak bundles; most of the mutant axons are not separated by the Schwann cell and remain directly apposed to each other. (G and H) are magnifications of Remak bundles seen in (D) and (E), respectively; bars: (A, B, D, and E), 2 μm; (G and H), 1 μm.

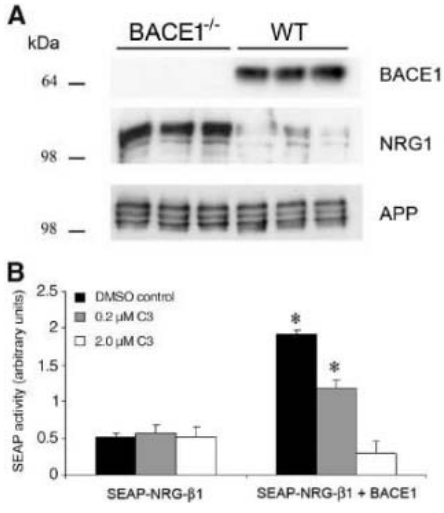

Fig. 3. Type III NRG1 is a physiological substrate for BACE1 in vivo. (**A**) Membrane preparations from brain lysates of 5-day-old wild-type (WT) and BACE1$^{-/-}$ mice were analyzed by immunoblotting with antibodies directed against the N-terminal domain of BACE1, a C-terminal domain of NRG1, or amyloid precursor protein (APP), as indicated. The full-length NRG1 precursor (130 kD) accumulates in *BACE1*$^{-/-}$ mice. (**B**) BACE1-dependent cleavage of SEAP–NRG1-β1 (*36*) was evaluated by SEAP assays with supernatants of control human embryonic kidney 293 (HEK293) cells (SEAP–NRG1-β1) or HEK293 cells coexpressing BACE1 (SEAP–NRG1-β1 + BACE1). A fourfold increase in shedding of the SEAP–NRG1-β1 fusion protein was measured upon BACE1 coexpression ($P < 0.001$). Shedding in coexpressing cells could be suppressed by applying the BACE1-specific inhibitor C3 (*37*). (*) Denotes significance compared to all other groups ($P < 0.001$; $n = 6$ independent measurements per group).

uncleaved NRG1 protein being due to loss of BACE1-dependent processing. The findings with BACE1$^{-/-}$ mice suggested that axonally bound type III NRG1 could be a physiological substrate for BACE1 in vivo. NRG1 isoforms with an EGF-β domain (NRG1-β) have a higher affinity for ErbB homo- and heterodimeric receptors and are thereby more potent in signaling than those with an EGF-α domain (NRG1-α) (*33*). The α-type NRG1 isoforms are dispensable, whereas the β-type isoforms are required for normal nervous system development (*34*). Consistent with this, the predominant NRG1 isoforms expressed in the nervous system were transmembrane isoforms with a β-type EGF domain (NRG1-β1) (*35*), which was confirmed for postnatal mouse brain by reverse transcription–polymerase chain reaction (fig. S4). To provide further evidence for BACE1-mediated processing of NRG1, we studied the release of secreted alkaline phosphatase (SEAP) proteins fused to NRG1-β1 sequences (*23*, *36*). Coexpression of SEAP–NRG1-β1 with BACE1 resulted in a strong increase ($P < 0.001$) in shedding of SEAP–NRG1-β1, which was inhibited in a dose-dependent manner by the BACE1-specific inhibitor C3 (*37*) (Fig. 3B). This result supports the hypothesis that BACE1 mediates the cleavage of NRG1-β1.

Our findings define a physiological function of BACE1. BACE1 is required for peripheral nerve myelination and axonal bundling by Schwann cells probably via processing of type III NRG1. However, other proteases and additional substrates can so far not be excluded. The tumor necrosis factor–α (TNF-α) converting enzyme (TACE), for example, is known to be the responsible shedding protease for some NRG1 splice variants (*26*, *36*, *38*, *39*) and other EGF receptor ligands (*40*). Previous evidence suggested that specifically cell surface–associated type III NRG1 is involved in neuron-glial signaling and peripheral nerve myelination (*26*, *41*). Our in vivo data suggest that neurons specifically trigger myelination and axonal sorting within Remak bundles by the proteolytic activity of BACE1. The data obtained with SEAP–NRG-β1 fusion proteins indicate that one recognition site for BACE1 resides in the stalk region of NRG1-β1 isoforms (present in types I and III). We cannot yet exclude the possibility that BACE1 activity results further in the complete release of type III NRG1 from the membrane via cleavage on the N-terminal side of the EGF domain. Whether BACE1 also plays important roles during myelination of the CNS remains to be shown, although accumulation of unprocessed NRG1 in the brain of BACE1$^{-/-}$ mice (Fig. 3A) may be indicative of a CNS function for BACE1.

The inhibition of β- and γ-secretase is currently one of the most hopeful approaches for AD therapy besides amyloid β-peptide vaccination (*2*, *42*–*44*). However, likely side effects due to the inhibition of physiological function of secretases must be carefully considered. Indeed, blocking γ-secretase function resulted in rather severe side effects due to the inhibition of Notch signaling (*2*). Our findings define a physiological function for BACE1 in myelination, which may allow monitoring of the effects for β-secretase inhibition in vivo.

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45. We thank Merck (X.-P. Shi) for the BACE1 inhibitor C3 and C. Blobel for pAPtag5-NRG1-β1. We also thank S. Lammich, C. Haffner, and C. Brösamle for helpful discussions and critically reading the manuscript. We especially thank C. Griffel and B. Erdmann (Max-Delbrück-Center) for technical support and advice on electron microscopical analysis of peripheral nerves. This work was supported by the Deutsche Forschungsgemeinschaft (SFB 596 "Molecular Mechanisms of Neurodegeneration" to C.H. and SFB 665 "Developmental Disturbances in the Nervous System" to C.B. and A.N.G.) and the Leibniz Award (to C.H. and C.B.), the NeuroNE (to C.H. and B.DeS.), the APOPIS Program (Abnormal proteins in the pathogenesis of neurodegenerative disorders—an integrated project funded by the European Union under the 6th Framework Programme), Priority: Life Science for health, Contract No. LSHM-CT-2003-503330 (to C.H. and B. DeS.), the Ernst-Jung Award for Medicine (to C.H.), and the NGFN-2 (to C.H.). This study was also supported by the Alzheimer Forschungsinitiative (to A.R.), the Interuniversity Attraction Poles P5/19 of the Belgian Federal Science Policy Office (to B. DeS. and P.S.), and the Pioneer Award from the Alzheimer's Association and Geconcerteerde Onderzoeksactie (K.U. Leuven) (to B. DeS).

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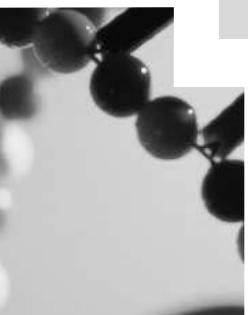

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Careers for Postdoctoral Scientists

Beyond the Ivory Tower

Moving from an academic environment to an industrial laboratory can prove difficult because of the need to adapt to a different culture. Here, we provide tips on how best to make a seamless transition. BY PETER GWYNNE

The majority of postdocs carry out their fellowships at universities, but large numbers find their first job in industry. The transition can prove difficult because of the different mindsets of academe and industry. Ph.D. scientists who choose to carry out their postdoctoral studies in industry face similar problems. However, companies can help to smooth the transition, and individual scientists can take their own steps to prepare for life outside the ivory tower. This supplement outlines some of those strategies.

A Lot of Commonality

The move from academe to commerce doesn't necessarily mean a definitive change of mindset for Ph.D.s who choose industrial postdoctoral projects and academic postdocs who set out on careers in industry. "There's a lot of commonality," says Linda Burkly, a distinguished investigator in molecular discovery at Biogen Idec. "The individual should have very strong scientific credentials and a strong research background. We are also working on cutting-edge research in the industrial community."

Stanley Crooke, CEO of Isis Pharmaceuticals, points out other resemblances between the two types of organization. "If industry is recruiting scientists at the postdoctoral level, it wants them to be scientists; we're not interested in their being business people," he explains. "And the demands of a good industrial lab are very similar to those of a good academic lab."

However, scientists who move from the ivory tower to the commercial world must prepare to fit into a different culture. "There tends to be a bit more structure in industry," Crooke says. CONTINUED »

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2) Construct bio-mimetic surfaces and self-assembled structures that permit external control of biological and biotechnological processes, such as, cell adhesion and cell cycle regulation.
BIOCONTROL offers first class scientific and complementary training to coach 'life science' experts who learn to work across disciplines.
BIOCONTROL expects high motivation to work on an interdisciplinary field, extraordinary communication skills and the readiness to work at different host institutions.

Please send your application **(by naming the position you are interested in)** including CV and references (as pdf-file) within 14 days after appearance of this advertisement to the network coordinator R. Willumeit: regine.willumeit@gkss.de (only email applications will be considered). **Starting date of the positions between 01.01.2007 and 01.04.2007** (duration initially limited to 3 years).
Note: Due to the strict regulations of the Marie-Curie-Training Networks - which aims at the mobility of people - only persons who do not have the citizenship of the supervising institutions can apply for the positions. For details **please contact http://biocontrol.tau.ac.il!**

GKSS is an equal opportunity/affirmative action employer seeking to increase the proportion of female faculty members. Qualified women are therefore especially encouraged to apply.
Handicapped persons with equal qualifications will be preferred.

The open positions are in detail:

Topic 1: Hydration and charge effects on membrane structure and interaction
Position WP1_1:
Place of work: Royal Institute of Technology (KTH), Department of Chemistry, Surface Chemistry in Stockholm, Sweden; frequent visits at SDU, Denmark.
Contact person: Prof. Per Claesson (per.claesson@surfchem.kth.se)
Project description: The PhD-project will include direct measurements of interactions between lipid layers of relevance for biological membranes and aims at finding correlations between short-range interactions, hydration state of lipid layers and adsorption properties of peptides to lipid layers. A range of modern techniques will be employed.
Requirements: Completed undergraduate studies in the area of chemistry, biochemistry or physics. Good knowledge in physical chemistry and interest in experimental cross-disciplinary work.

Position WP1_2:
Place of work: University of Southern Denmark (SDU), Department of Physics and Chemistry, Odense, Denmark; frequent visits at KTH, Sweden.
Contact person: Prof. Beate Kloesgen (kloesgen@memphys.sdu.dk)
Project description: The project will involve the application of a spectrum of diverse modern techniques for the study of hydration and charge effects as precondition/control tool for the interaction among model membranes or for the association of (macro)molecules to biointerfaces.
Requirements: Master degree in physics or physical chemistry; interest for basic biophysical studies is needed.

Topic 2: Peptide interactions with bio-mimetic membranes
Position WP2_1:
Place of work: Ben Gurion University, Beer Sheva, Israel for 18 month and the University of Aarhus, Denmark for 18 month
Contact person: Prof. Raz Jelinek (razj@bgumail.bgu.ac.il) or Prof. Niels Chr. Nielsen (ncn@inano.dk)
Project description: The student will be working on bio-mimetic membranes. Research will be both fundamental as well as applied, and involve preparation and characterization using advanced spectroscopic and microscopic techniques, such as fluorescence spectroscopy and, in particular, liquid- and solid-state NMR spectroscopy.
Requirements: Master in either chemistry/biochemistry/biotechnology.

Topic 3: Single bioactive peptides at artificial and biological membranes
Position WP3_1:
Place of work: Institut für Physikalische und Theoretische Chemie, Rheinische Friedrich-Wilhelms-Universität Bonn, Germany
Contact person: Prof. Ulrich Kubitscheck (u.kubitscheck@uni-bonn.de)
Project description: Analysis of mobility and clustering of bioactive peptides in model and cell membranes by single molecule microscopy.
Requirements: Diploma or equivalent in physics, chemistry or biology. Interest in, better experience with quantitative light microscopy.

Topic 4: In silico investigation of peptide-membrane interactions
Position WP4_1:
Place of work: Tel-Aviv University, Israel
Contact person: Prof. Nir Ben-Tal (bental@ashtoret.tau.ac.il)
Project description: This interdisciplinary research project involves the development of computational methodology for the study of peptide-membrane interaction, and the use of the new methodology in combination with existing methods to investigate selected antimicrobial, fusion and amyloidic peptides. The project will be conducted in close collaboration with some of the experimental members in the consortium, and includes visits in their labs.
Requirements: A university degree in biology, chemistry, physics or similar field, and the curiosity to understand the fundamentals of peptide-membrane energetics as well as the relevant biology.

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Position WP4_2:
Place of work: GKSS Research Centre Geesthacht, Geesthacht (near Hamburg), Germany, Frequent visits at the partner laboratory at Tel-Aviv University, Israel.
Contact person: PD Dr. Regine Willumeit (regine.willumeit@gkss.de)
Project description: In close collaboration with the Tel-Aviv University the student will synthesize, characterize and study the interaction of computational predicted synthetic peptides with model membranes. Beside measuring the bacterial, cytotoxic and haemolytic activity the student will apply several scattering and spectroscopic techniques.
Requirements: University degree in biochemistry or biology with the capability to work at large scale research instrumentation.

Topic 5: Fusion and domain formation in biomembranes
Position WP5_1:
Place of work: Paul Scherrer Institute, Villingen, Switzerland, for 18 month, afterwards at Niels Bohr Institute, Kopenhagen, Denmark for 18 month.
Contact person: Dr. Thomas Gutberlet (thomas.gutberlet@psi.ch) or Prof. Thomas Heimburg (theimbu@nbi.dk)
Project description: The project deals with the study of domain formation and fusion processes in biological model membrane systems. Main techniques to be used in this project involve X-ray and neutron scattering, fluorescence microscopy, AFM and calorimetry.
Requirements: University degree in physics, biophysics, biochemistry or chemistry with strong interest in physics of biomembranes.

Topic 6: Interaction of cytotoxic peptide aggregates with the lipid membrane
Position WP6_1:
Place of work: Université Libre de Bruxelles, Brussels, Belgium for 18 month and University Louis Pasteur, Strasbourg, France for 18 month.
Contact person: Prof. Jean-Marie Ruysschaert (jmruyss@ulb.ac.be) or Prof. Burkhard Bechinger (bechinger@chimie.u-strasbg.fr)
Project description: Structural investigation of the membrane interactions of cytotoxic peptide aggregates like Alzheimer peptides.
Requirements: University degree in chemistry, physics or biochemistry; interest in biophysical approaches (in particular NMR spectroscopy).

Topic 7: Structure and translocation of peptide-DNA transfection complexes
Position WP7_1:
Place of work: University Louis Pasteur, Strasbourg, France for 24 month and Department of Crystallography, Birkbeck College, University of London, and Daresbury Laboratory, UK for 12 month.
Contact person: Prof. Burkhard Bechinger (bechinger@chimie.u-strasbg.fr) or Prof. Bonnie Wallace (b.wallace@mail.cryst.bbk.ac.uk)
Project description: Investigation of the structural basis of the mechanism of transfection of DNA and siRNA for therapeutic approaches by using and developing new methodologies in synchrotron radiation circular dichroism (SRCD) or other novel spectroscopic techniques.
Requirements: Chemist, physicist or biochemist with interest in biophysical approaches in particular synchrotron CD and NMR spectroscopy.

Topic 8: Membrane-active peptides as anticancer therapeutics
Position WP8_1:
Place of work: Institute of Biophysics and Nanosystems Research, Graz, Austria for 24 month and GKSS Research Center Geesthacht, Geesthacht (near Hamburg), Germany for 12 month.
Contact person: Univ. Doz. Karl Lohner (karl.lohner@oeaw.ac.at) or PD Dr. Regine Willumeit (regine.willumeit@gkss.de)
Project description: The aim is to deliver essential information for the development of potent anticancer peptides. The candidate will elucidate the membrane composition of cancer cells, determine the phase behaviour of respective model membranes and their interaction with membrane-active peptides. This will be complemented by biological activity testing.
Requirements: University degree in biochemistry, biology or physics with a strong biophysical interest.

Topic 9: Property-controlling enzymes at membrane interfaces
Position WP9_1:
Place of work: Stockholm University, Stockholm, Sweden for 24 month and Université Libre de Bruxelles, Brussels, Belgium for 12 month.
Contact person: Prof. Åke Wieslander (ake@dbb.su.se) or Prof. Jean-Marie Ruysschaert (jmruyss@ulb.ac.be)
Project description: Control and regulation of membrane bilayer packing properties. We want to unravel how membrane interface enzymes sense bilayer properties and synthesize the proper membrane lipid constituents. These bilayer properties are essential for the function of many membrane proteins. The enzymes, at the peptide segment and full-size protein levels, will be analyzed by a variety of biochemical (including mol. genetic), bioinformatic, and spectroscopic techniques.
Requirements: The candidate should have a good background in chemistry, with focus on biochemistry. Experience in molecular biology is of high advantage.

Topic 10: Self-assembly structures to control biomolecular function
Position WP10_1:
Place of work: Lund University, Sweden for 18 month and University of Southern Denmark, Odense, Denmark for 18 month.
Contact person: Prof. Tommy Nylander (Tommy.Nylander@fkem1.lu.se) or Prof. Beate Kloesgen (kloesgen@memphys.sdu.dk)
Project description: Modern structure analysis methods centred around transmission electron microscopy and X-ray and neutron diffraction will be applied to study new lipid based materials for controlled drug administration. Accomplishing methods: DSC, AFM, fluorescence microscopy.
Requirements: Master degree in physics or chemistry (with focus on physical chemistry) or biochemistry (focus on biophysical chemistry).

Topic 11: Cell-to-bio-mimetic interface interactions
Position WP11_1:
Place of work: Malmö University (PhD in biomedical technology), Sweden for 24 month and GKSS Research Center Geesthacht, Germany for 12 month.
Contact person: Prof. Thomas Arnebrant (Thomas.Arnebrant@hs.mah.se) or PD Dr. Regine Willumeit (regine.willumeit@gkss.de)
Project description: The aim of this PhD project is to monitor and control the cellular interaction with bio-mimetic interfaces (i) by characterising focal adhesion complexes of adherent eukaryotic cells by electrical impedance, ellipsometric, AFM and QCM measurements, (ii) by changing bio-mimetic bio-interfaces to control characteristics of focal adhesion complexes and (iii) by correlating characteristics of focal adhesions with metastatic potential of cancer cells and tissue-implant interactions.
Requirements: The candidate should have excellent basic education in chemistry or biochemistry. Knowledge in cell biology is of high advantage.

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Careers for Postdoctoral Scientists

Roberto Polakiewicz, chief scientific officer of Cell Signaling Technology, points out that the cultures of different corporations can vary markedly. However, he says, "The main issue is that you're coming from an environment where there's academic freedom. In the university, you can choose your project, as long as it's funded, and you do your work. You're encouraged to have a lot of interaction with your fellow postdocs. In industry it varies. Some pharmaceutical companies have very open-ended projects. But generally there's less academic freedom and more restriction to a project."

Patricia Andrade-Gordon, vice president for biology research and early development at Johnson & Johnson Pharmaceutical Research & Development, points out that the industrial environment involves positives and negatives when compared with the ivory tower. "In industry, while you have access to more resources, you also have less flexibility to choose your research area, as your goals are linked to company focus," she says. "Time management is likely the greatest challenge faced during the transition from academia to industry. In industry, objectives are defined for the year, and performance is directly linked to your ability to deliver against those goals, whereas academic postdocs may have more flexibility."


LINDA BURKLY

Industrial Attitudes

Industrial attitudes toward teamwork can also challenge academic postdocs who become new employees. "The main difference is the degree to which we work in teams in the industrial setting. There are project teams organized to investigate molecular pathways and advance therapeutic targets to a development stage," Burkly notes. "This is new in some respects to academic postdocs. They may be used to networking and collaborating in their labs, but the main difference in industry is the team environment. Teams are composed of scientists with different backgrounds and expertise, brought together to energize and move things more quickly toward the goal – the development stage. When postdocs or new employees get onto a project team, they may find it hard to figure out their roles on the team – how they are supposed to function and provide leadership with respect to their own skills."

Polakiewicz echoes that sentiment. "In academic labs it's more individual work," he explains. "In industry, postdocs may see themselves in a team situation in which they have to do certain things. They are company projects, not their own, although the situation varies from company to company."

Alyson Reed, executive director of the National Postdoctoral Association (NPA), confirms the importance of industrial teamwork from the point of view of the postdocs themselves. "We've heard from some of our members who are engaged in basic research that the differences are in terms of the team effort," she says. "In the academic environment, there's much more independence and more opportunity to pursue your own ideas. In industry, new ideas are evaluated on the basis of the company's overall goals and commercial needs. So you need to coordinate your work much more with others in your research team than you would in academia." On the other hand, Reed points out, "There is a trend in academia toward more collaboration and teamwork."

Academics who move into industry, whether before or after working on their postdoctoral projects, face a particularly substantive issue that has strong impact on their mode of thinking. "You have to grapple with the publishing policy, particularly if you are in an industrial postdoc program," Crooke says.


STANLEY CROOKE

A Different Sense of Community

Scientists who choose to do their postdoctoral work in industry must deal with another significant alteration in mindset. "Another major change to account for is the difference found in most industrial environments as compared with academia," Andrade-Gordon says. "The same sense of academic community does not exist, for the most part, for the industrial postdoc, unless there are significant numbers of postdocs within a given department. This can present a major challenge for maintaining that sense of common-ground community found in academia, where you are surrounded by other postdocs, graduate students, and professors, all with similar pressures."

Reed echoes that point. "Informal enquiries show that our members found a larger community of people to interact with in the academic environment," she says. "They could assume that certain core facilities would be available. It was easier for them to stay current with research in their areas; you can't assume that in industry."

On the other hand, industry seeks and values the new ideas that incoming or former postdocs can bring from the academy. "When I was in R&D at SmithKline in 1981, I put probably the first postdoc program into industry," Crooke recalls. "One of the fundamental reasons that academic scientists seem to have longer careers before they become outdated is that they have reactions with new blood. So I felt a postdoc program would delay the obsolescence of our R&D people. It would also give us an opportunity to identify outstanding candidates for jobs, and vice versa. Also, there's no place to learn drug discovery and development except in the pharmaceutical industry."

The learning process can lead to a dead end. "It's probably a one-way road when you switch to industry," Polakiewicz asserts. "An industrial postdoc implies that you'll stay in industry, because it's harder to publish high-profile papers. Some companies have restrictions on publishing." CONTINUED »

Careers for Postdoctoral Scientists

Of course, many scientists who transfer from academia to industry have given the move plenty of thought. "I haven't experienced new employees having particular difficulties finding their place," Biogen Idec's Burkly says. "In the process of making their decision to leave the academic community and come to industry, they have asked many questions, identified key differences, and shown themselves to be aware of the way industrial projects are managed."


ALYSON REED

Do You Belong?

How should young scientists go about deciding whether or not they belong in industry? "The acid test is to question what you want to do with the information you have on enzyme X," Crooke says. "Do you want to spend you life on it or to engage in enzyme X with an application in mind? I had a postdoc or two who had highly focused interests; they wanted to know about DNA polymerase rather than wanting to know about DNA polymerase so that they could use it to make a drug. They were not ready for industry."

Polakiewicz makes the point more pithily. "You should have a very good self-explanatory process, specifically with what you want to do and the sort of career path you want," he says. "More often than not, the decision is a point of no return."

That process should include a personal inventory. "The first thing is to bring an asset of skills that have value; you had better know something," Crooke says. "Second, have a respect for the process. The two tough things in life are being a good parent and making a drug. So a postdoc should come in with respect for the drug discovery and development process. Don't come in if you are looking for a place to park or to make money. The person who cares and commits is successful."

Scientists should take care to prepare for the interview with a potential industrial employer or postdoctoral supervisor. "If you're interviewing for a specific position, ask very detailed questions about expectations, resources you'll have access to, and how your work will fit into the larger goals of the company," the NPA's Reed advises. "Be very savvy about what you're going to be asked to do."

The NPA also has advice for postdocs who think that they might want to work in industry. "If you're not interviewing for a specific job, we recommend informational interviewing about what a job in industry might entail and what type of facilities you might expect," Reed says. "Many companies consider this informational interviewing perfectly acceptable and valid."

Visit **www.sciencecareers.org** and plan to attend upcoming meetings and job fairs that will help further your career.

The Corporate Interview

Certainly corporate interviewers take all their conversations with young scientists seriously. "As someone who interviews a lot of potential hires, I try to make sure that the individual is well suited to the situation," Biogen Idec's Burkly says. "You want the individual to be happy and you want to be happy with him or her. Even if candidates don't realize what questions to ask, you try to get them to understand what they're getting into."

Successful interviews represent just the start of a process of introducing young scientists to the industrial life. "When they have started in their new position, they're mentored by their line manager and project leader," Burkly continues. "They have the opportunity to meet and talk with peers and colleagues who will be on their project team to get an understanding of the history of their project and the various perspectives that other scientists bring to it. In this way they can get a sense of where each person on the team is coming from and how they themselves can bring value."

Industrial managers agree that effective mentoring is critical. "For academic postdocs, the transition needs to be on the job, aided with the help of mentoring programs," says Johnson & Johnson's Andrade-Gordon. "Pairing a postdoc with an experienced employee to shadow and learn from has proven to be a very successful model for us." Beyond that, she adds, "We take career development very seriously. The success of newly hired scientists is part of the accountability of their supervisors. We have our First Friend program, which identifies a permanent employee from the same department or team to welcome the new employee and to assist him or her with making introductions to others, as well as helping with passwords, training, learning the new systems and databases, and obtaining information on who to go to when questions arise."

Special Care and Feeding

Scientists who carry out their postdoctoral studies in industry require special care and feeding. "The principal responsibility is between the supervisor and the postdoc," Crooke of Isis Pharmaceuticals explains. "We have a technology base that takes a while to learn. Every day we have people making presentations of their work and program reviews. Postdocs are expected to participate in them and learn from them. You learn by osmosis to do what you do well and to understand how it fits in the process."

Reed sums up what a Ph.D. or postdoc might expect at the start of research in an industrial lab. "We're not aware of any structured or defined transition programs," she says. "But like most jobs, if you're coming into an entry-level position, there's a certain amount of on-the-job training – whether you've been in academia or any other kind of setting."

A former science editor of Newsweek, *Peter Gwynne (pgwynne767@aol.com) covers science and technology from his base on Cape Cod, Massachusetts, U.S.A.*

POSITIONS OPEN

POSTDOCTORAL POSITIONS (four) at University of Minnesota (UMN), Hormel Institute **(Rhoderick E. Brown, Principal Investigator)** to investigate in vitro and in vivo functions of sphingolipid binding/transfer proteins and glycosphingolipid organization in membranes. Sphingolipid transfer protein structure-function to be analyzed by fluorescence, circular dichroism, and X-ray diffraction. Experience with preceding approaches preferred including cloning, point mutagenesis, protein purification, refolding, and crystallization. In vivo functionality of sphingolipid transfer/binding protein to be studied using immunological, kinase-related signaling, two-hydrid, RNAi, and transgenic approaches. Sphingolipid interactions with membrane lipids to be studied by fluorescence, monolayer, and calorimetric approaches. Strong background with preceding approaches preferred. Require Ph.D. in biochemistry, molecular biology, biophysics, or related discipline. If interested, apply online at **website: http://www.umn.edu/ohr/employment** (UMN employment home page) and refer to requisition number 144223 when entering curriculum vitae and names of three references. *The University of Minnesota is committed to the policy that all persons shall have equal access to its programs, facilities, and employment without regard to race, color, creed, religion, national origin, sex, age, marital status, disability, public assistance status, veteran status, or sexual orientation.*

NIH-funded **POSTDOCTORAL POSITION** in mathematical and computational modeling of infectious diseases is available immediately within the Division of Infectious Diseases, University of Pittsburgh, to study the impact of antiretrovirals on the spread of human immunodeficiency virus (HIV). Candidates should have a Ph.D. in mathematics, engineering, physics, computer science, or related field. Proficiency in advanced programming languages such as C++ and Java is required. Excellent mathematical skills in modeling time progressing phenomena, knowledge of parameter estimation techniques and experience in individual-based simulation are essential. A working knowledge of mathematical, statistical and simulation software is preferable. Send curriculum vitae and three references to: **Dr. Ume L. Abbas. E-mail: abbasu@dom.pitt.edu; Telephone: 412 648 6401; fax: 412 648 6399.** *The University of Pittsburgh is an Affirmative Action, Equal Opportunity Employer.*

One to two **POSTDOCTORAL POSITIONS** are available immediately in the Duke Institute for Genome Sciences and Policy. Highly motivated recent Ph.D.s with a background in molecular biology, parasitology, or erythrocyte biology are encouraged to apply. The successful candidate will be using the state-of-the-art genomic tools and advanced bioinformatics to dissect the cancer microenvironments, diseased phenotypes of hemoglobinopathies, and host-pathogen interaction between *Plasmodium*. Experiences in mammalian tissue culture, fluorescence activated cell sorter analysis, molecular biology are required. Strong team-working capabilities, good communications skills, and ability to conduct independent research are essential. Interested candidates should send by e-mail a cover letter, curriculum vitae, and contact information of three references to: **Jen-Tsan Ashley, Chi, Ph.D., e-mail: chi00002@mc.duke.edu.**

POSTDOCTORAL RESEARCHER

The Division of Cardiothoracic Surgery at the Ohio State University Medical Center is seeking applications for Postdoctoral Researchers from candidates with Ph.D. degree to work on areas related to cardiovascular diseases. On-hand experience in molecular biological techniques required. Candidates with expertise in any of the following areas will be preferred: gene expression studies related to atherosclerosis, macrophage biology, and oxidative stress. Send application, date of availability, curriculum vitae, and cover letter to **Dr. Parthasarathy** at **e-mail: spartha@osumc.edu.** *The Ohio State University is an Equal Opportunity/Affirmative Action Employer.*

POSTDOCTORAL OPPORTUNITIES

The Wadsworth Center of the New York State Department of Health, with basic and applied research programs in the biomedical and environmental sciences, provides a unique and dynamic postdoctoral training experience. Enhancing this environment are state-of-the-art core facilities; broad-based graduate programs with the University at Albany, State University of New York; and new initiatives in bioinformatics, genomics, nanobiotechnology, and biodefense. Positions are available in the following areas:

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- **Carcinogenesis**
- **Cell Biology/Mitosis**
- **DNA Repair/NMR**
- **Drug Metabolism/Resistance**
- **Gene Expression/Regulation**
- **Immunology**
- **Infectious Disease**
- **Medical Entomology**
- **Microbial Genetics/Pathogenesis**
- **Mobile Genetic Elements**
- **Neuroscience/Disease**
- **Stem Cell Biology**
- **Structural Biology**
- **Toxicology/Neurotoxicology**

For additional information, go to:
www.wadsworth.org/educate/postdocs.htm
and to apply, contact:
Dr. Donal Murphy, Research Office,
Wadsworth Center, New York State Department of Health
P.O. Box 509, Albany, NY 12201-0509
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Sr. Research Chemist / Research Fellow – RNAi – Vaccine & Biologics Research

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Incumbent will perform independent research into the design and use of liposomes as novel biomolecule delivery systems. Primary responsibilities will include: (1) application of lipid chemistry to the design, formulation, and characterization of novel liposomes for encapsulation of oligonucleotides or other biomolecules, (2) design and implementation of methods to selectively label or tag liposomes, (3) development of novel liposome-based systems to optimize release of cargo upon delivery to a biological system, (4) supervision of 1-2 associate-level scientists, and (5) preparation of manuscripts for the publication of scientific information, patent application, and required internal documentation.

The primary responsibilities of the position require a thorough working knowledge of lipid chemistry and biochemistry, as well as current techniques and practices for the preparation of liposomes suitable for use in *in vitro* and *in vivo* biological systems. A particular focus of this work is expected to be the development of novel lipid systems which are able to optimize the encapsulation, stabilization, and release of therapeutic oligonucleotides *in vivo*. It is expected that the candidate will be knowledgeable in the area of chemical manipulation and modification of lipids and willing to develop novel approaches where required. Concomitant with this, a strong background in methods related to the analysis of lipid size, structure, and stability will be highly desirable.

The successful candidate will hold a Doctor of Philosophy degree in Chemistry, Biochemistry or a related discipline with an excellent academic history, strong publication record, and preferably 3 + years' post-degree experience. It is expected that approximately 50% of the candidate's responsibilities will involve hands-on benchwork with experimental design, data interpretation, and administrative duties comprising the remainder. The successful candidate will have a focused background in the general field of lipid biochemistry with a good working knowledge of current techniques for the preparation of liposomes. The candidate will be expected to show a high degree of interest in the identification and development of novel or proprietary liposomal formulations which can optimize stability and delivery efficiency of cargo molecules. Relevant liposomal modification experience would include a working knowledge of methodologies to introduce site-specific fluorescent labels, PEGylation, and other derivatives. Desirable analytical skills relevant to product characterization would include proficiency in sizing methods, fatty acid analysis, and spectroscopy. The candidate is expected to show a high degree of motivation and be able to work with a high degree of independence. Required managerial skills include the ability to design experiments, communicate the necessary information to associates for implementation, and track results. He/she should be able to effectively communicate scientific information with a good previous history of publication in peer-reviewed journals. The candidate must be willing to take responsibility for preparation of patents on novel methodology and manuscripts for publication. Familiarity with current Good Laboratory Practices (GLP) would be considered useful.

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Indiana University School of Medicine

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Sr. Research Chemist / Research Fellow – RNAi – Vaccine & Biologics Research

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Incumbent will perform independent research into the design and formulation of biocompatible nanoparticles as novel delivery systems for therapeutic RNA oligonucleotides. Primary responsibilities will include: (1) design, formulation, and purification of nanoparticles using established or novel methodologies, (2) design and implementation of methods to stabilize and accurately characterize nanoparticle preparations, (3) development of novel targeting methods to effect delivery of nanoparticle-RNA complexes to specific in vivo targets, (4) supervision of 1-2 associate-level scientists, and (5) preparation of manuscripts for the publication of scientific information, patent application, and required internal documentation.

The primary responsibilities of the position require a thorough working knowledge of current techniques and practices for the preparation of biomolecule-derived nanoparticles suitable for use with *in vitro* and *in vivo* biological systems. A particular focus of this work is expected to be lipid-based delivery vehicles, and it is expected that the candidate will be able to apply formulation expertise to the production of products which are amenable to further derivatization with a targeting molecule of choice (i.e., ligand, peptide, antibody). Concomitant with this is a strong background in particle sizing methodologies, bioconjugate chemistries, and analytical techniques

Qualifications

The successful candidate will hold a Doctor of Philosophy degree in Biochemistry or a related discipline with an excellent academic history, strong publication record, and preferably 3+ years' post-degree experience. It is expected that approximately 50% of the candidate's responsibilities will involve hands-on bench work with experimental design, data interpretation, and administrative duties comprising the remainder. The successful candidate will have a focused background in the preparation of particulate delivery systems such as liposomes, proteoliposomes, uni- and multilamellar vesicles, and polycationic complexes. Relevant target-enabling experience would include a working knowledge of current methodologies for covalent and non-covalent incorporation of peptides, proteins, and other biomolecules into nanoparticles., Desirable analytical skills relevant to product characterization would include proficiency in sizing methods such as light scattering, size exclusion chromatography, and differential centrifugation. The candidate is expected to show a high degree of motivation and be able to work with a high degree of independence. Required managerial skills include the ability to design experiments, communicate the necessary information to associates for implementation, and track results. He/she should be able to effectively communicate scientific information with a good previous history of publication in peer-reviewed journals. The candidate must be willing to take responsibility for preparation of patents on novel methodology and manuscripts for publication. Familiarity with current Good Laboratory Practices (GLP) would be considered useful.

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To be considered for this position, please visit our career site at **www.merck.com/careers** to create a profile and submit your resume for requisition # **BIO001275**. Merck is an equal opportunity employer, M/F/D/V – proudly embracing diversity in all of its manifestations.

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NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

Research Associateship Program

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Detailed program information, including instructions on how to apply, is available on the NRC Web site at :
www.national-academies.org/rap

Questions should be directed to :
National Research Council
TEL: (202) 334-2760
E-MAIL: rap@nas.edu

Qualified applicants will be reviewed without regard to race, religion, color, age, sex or national origin.

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

AWARDS

Children's Tumor Foundation
Ending Neurofibromatosis Through Research

YOUNG INVESTIGATOR AWARDS

Pre- and Postdoctoral Grants for Neurofibromatosis Research

NF is comprised of three distinct genetic disorders: NF1, NF2 & Schwannomatosis. Occurring in 1-3,500 births, NF causes tumors to grow anywhere in the nervous system. NF can lead to bone deformities, learning disabilities, deafness and blindness. Though many of the signals affected in NF are well known - e.g. Ras/PI3K/mTOR/Mek/Erk/Rac/Pak - much remains to be learned and there are currently no effective NF therapeutics.

The Children's Tumor Foundation is offering up to 10 Young Investigator Awards to encourage outstanding pre- and post-doctoral researchers to pursue careers in NF research. The two-year awards offer NIH-equivalent funding levels (max 45k/yr) plus up to $5,000 support to attend scientific meetings. There is no citizenship requirement, and we encourage proposals into all forms of NF and their complications.

Intent to Submit Application (first 2 pages)
Due: February 14th, 2007
Full Application Due: April 1st, 2007

Full RFA & Application Materials:
http://www.ctf.org/professionals/yia.htm

More information: Min Wong, Research Program Director:
mwong@ctf.org

CONFERENCE 2007
THE CHILDREN'S TUMOR FOUNDATION

The 2007 NF Conference: **June 10-12, Park City, UT**
Learn more at **www.ctf.org**

POSTDOCTORAL OPPORTUNITIES

Reginald A. Daly Postdoctoral Fellowship
Harvard University
Department of Earth and Planetary Sciences

The Department of Earth and Planetary Sciences at Harvard University invites applicants for the Reginald A. Daly Postdoctoral Research Fellowships.

The Department seeks outstanding candidates in the broad field of Earth and Planetary Sciences. **We encourage applications of candidates pursuing field observations, lab-based science, and theory, and interested in geology, geochemistry, ocean, atmosphere and climate dynamics and chemistry, seismology, geophysics, planetary sciences, and other related fields.** These honorific postdoctoral fellowships are awarded for a one-year period, with an anticipated extension for a second year. Daly fellows carry out independent research, yet are encouraged to interact with one or more research groups in the department. Applicants are welcome to contact members of the department before applying. Applications should include a curriculum vitae, names and affiliation of three referees, a one page statement of the applicant's doctoral research, and a one to two page postdoctoral research proposal. Applications are due **January 15, 2007**. Applicants are responsible for contacting the referees to have their letters arrive directly at the address below by the **January 15, 2007** deadline. Send applications (email preferred) to: **Daly Postdoctoral Search Committee, c/o Rady Rogers (rmrogers@fas.harvard.edu), Department of Earth and Planetary Sciences, Harvard University, 20 Oxford Street, Cambridge, MA 02138.**

The annual salary is $52,000 with additional funds of $15,000 available for research support over a two-year period. Applicants should have a recent Ph.D. or should be 2007 degree candidates. Completion of the Ph.D. is required by the time of the appointment. For more information about the department and Daly postdoctoral program, please visit **http://www.eps.harvard.edu/daly.php**.

We particularly encourage applications from women and minorities. Harvard University is an Affirmative Action/ Equal Opportunity Employer.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Postdoctoral Positions

The University of Alabama at Birmingham (UAB) is one of the premier research universities in the US with internationally recognized programs in AIDS and bacterial pathogenesis, bone biology and disease, cancer, diabetes and digestive and kidney diseases, free radical biology, immunology, lung disease, neuroscience, trauma and inflammation, and basic and clinical vision science among others. UAB is committed to the development of outstanding postdoctoral scientists and is one of the first universities to establish an office of postdoctoral education.

UAB is recruiting candidates for postdoctoral positions in a variety of research areas. UAB faculty are well funded (20th in 2005 NIH funding), utilize multidisciplinary approaches, and provide excellent research training environments that can lead exceptional candidates to entry level positions in academia, government or the private sector. Full medical coverage (single or family), competitive salaries/stipends, sick leave, vacation, and maternity/paternity leave are offered with every position. Depending on the source of funding, other benefits may be available. Birmingham is a mid-size city centrally located in the southeast near beaches and mountains and enjoys a moderate climate for year round outdoor activities and a cost of living rate lower than most metropolitan areas.

Visit our web site at **www.postdocs.uab.edu**, under Postdoctoral Opportunities to view posted positions. Alternatively, you may send us your CV and cover letter with research interests (PDF only) to **postdocs@uab.edu** and we will post this on our web site so that investigators may contact you. **University of Alabama at Birmingham, Office of Postdoctoral Education, 205-975-7020**.

UAB is an Equal Employment Opportunity Employer.

POSITIONS OPEN

CHAIR, DEPARTMENT OF PHYSIOLOGY
EMORY UNIVERSITY SCHOOL OF MEDICINE

Emory University School of Medicine announces a search for the Chair, Department of Physiology. Emory University School of Medicine, a component of Emory's Robert W. Woodruff Health Sciences Center, is ranked among the nation's finest institutions for biomedical research and education. The 325,000-square-foot Whitehead Biomedical Research Building, which opened in 2002, provides laboratory and administrative space for the Department. The faculty members maintain active research programs utilizing state of the art technology and model systems to address basic questions of cell and molecular signaling, spinal cord neurophysiology and biophysics, with heavy reliance on quantitative biology and bioinformatics. The Chair will provide innovative leadership in all research and educational endeavors in the Department of Physiology and be responsible for the continued development of an academically distinguished department. We seek a recognized leader with an outstanding academic background, a vision for contemporary physiology in the coming decades, and the ability to advance and encourage exceptional programs in basic and translational research in physiology.

Please send (preferably electronically) curriculum vitae and names and contact information of three references to the **Physiology Chair Search Committee, c/o Office of the Dean, Emory University School of Medicine, 1440 Clifton Road, N.E., Ste. 321, Atlanta, Georgia 30322, attn: Ms. Linda Townsend (ltownsend@emory.edu).**

Emory University is an Equal Opportunity, Affirmative Action Employer. Women and members of minority groups are strongly encouraged to apply.

EMORY UNIVERSITY

University of Florida
College of Medicine
Department of Medicine
Division of Nephrology, Hypertension and Renal Transplantation

The University of Florida Division of Nephrology, Hypertension and Renal Transplantation seeks nominations and applications for the R. Glenn Davis Endowed Chair in clinical investigation. This is a full-time, tenure-accruing faculty appointment at the rank of Associate or full Professor. The successful candidate will be expected to develop and lead a major clinical and translational research program in nephrology, hypertension or a related discipline. Appropriate resources will be provided to support the effort. Candidates must possess an M.D. or M.D./Ph.D., be board eligible or board certified in their specialty and have a proven record of extramurally funded clinical investigation. Salary and academic rank will be commensurate with the individual's training and experience. The anticipated start date for this position is March, 2007. Interested parties should forward a curriculum vitae with three letters of recommendation to:

C. Craig Tisher, M.D.
Chair, Search Committee
Division of Nephrology, Hypertension and Renal Transplantation
PO Box 100224
Gainesville, FL 32610
tisher@dean.med.ufl.edu

The review of applications has already begun and will continue until the position is filled. Please complete the optional Data Applicant Card at **www.hr.ufl.edu/job/datacard.htm**, reference job requisition number **037051**.

The University of Florida is an Equal Opportunity Employer. Women and minorities are encouraged to apply.

Department of Health and Human Services
National Institutes of Health
National Institute of Mental Health

Director, Division of Adult Translational Research and Treatment Development

The National Institute of Mental Health, a major research component of the National Institutes of Health (NIH) and the Department of Health and Human Services (DHHS), is seeking exceptional candidates for the position of Director, Division of Adult Translational Research and Treatment Development (DATR). This position provides overall scientific, programmatic, and administrative leadership for an extramural grants and contracts portfolio of approximately $232 million and manages a staff of 24 individuals (http://www.nimh.nih.gov/datr/datr.cfm). The DATR Director is responsible for developing a vision for research and training aimed at understanding the pathophysiology of mental illness and hastening the translation of behavioral science and neuroscience advances into innovations in clinical care and prevention strategies.

Applicants must possess an M.D. with a specialty in psychiatry and/or a Ph.D. in neuroscience, psychology, or related discipline with broad senior-level research experience and experience in direct administration of a research program. Applicants should be known and respected within their profession, both nationally and internationally, as distinguished individuals of outstanding scientific competence. Salary is commensurate with experience and accomplishments.

Interested candidates should send a letter of interest, including a brief description of research experience, contact information for at least three references, and a curriculum vitae and bibliography to: **Dr. Richard Nakamura, Chair, Search Committee for Director, DATR, at NIMHsearch@mail.nih.gov or at 6001 Executive Blvd. Room 8235, MSC 9669, Bethesda, MD 20892 (Rockville, MD 20852 for express or courier service)**. Review of applications will begin on **November 15, 2006**, but applications will continue to be accepted and considered until the position is filled.

The NIH encourages the application and nomination of qualified women, minorities, and individuals with disabilities.

Department of Health and Human Services
National Institutes of Health
Director, National Center for Research Resources and
Associate Director for Clinical Research (Extramural)

The Office of the Director, National Institutes of Health (NIH) in Bethesda, Maryland, is seeking applications from exceptional candidates for the position of Director, National Center for Research Resources (NCRR). The Director, NCRR, will also serve as the NIH Associate Director for Clinical Research (Extramural). NCRR, with a staff of approximately 100 employees and a $1 billion budget, is the focal point at NIH for biomedical, clinical and translational research resources. The incumbent serves as a principal advisor to the Director, NIH; participates in discussions relative to the development of major policy decisions affecting biomedical, clinical and translational research resources; provides advice and consultation to NIH components, advisory councils and grantee organizations and institutions; and assures that effective administrative procedures are established so that program operations and obligations of government funds and other resources are rendered consistent with statutory and regulatory requirements and within limitations imposed by the Department of Health and Human Services (DHHS) and Executive Branch policies. As Associate Director for Clinical Research (Extramural), the incumbent is expected to provide leadership for clinical research activities across the NIH. This leadership will involve the coordination of clinical research activities to enhance the integration of basic and clinical research. The Associate Director for Clinical Research will work closely with the other Institute and Center Directors to enhance the efficiency and effectiveness of clinical research supported by the NIH. Applicants must possess a Ph.D., M.D., or a comparable doctorate degree in the health sciences field plus senior level scientific experience and knowledge of biomedical, clinical and/or translational research programs in one or more health science areas. Salary is commensurate with experience and a full package of benefits (including retirement, health, life, long term care insurance, Thrift Savings Plan participation, etc.) is available. A detailed vacancy announcement, along with mandatory qualifications and application procedures, can be obtained via the NIH Home Page at: **http://www.jobs.nih.gov** under the Senior Job Openings section. Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, and Dr. David Schwartz, Director, National Institute of Environmental Health Sciences, will be serving as co-chairs of the search committee. Questions on application procedures may be addressed to **Ms. Regina Reiter at ReiterR@od.nih.gov or discussed with Ms. Reiter by calling 301-402-1130**. Applications **must** be received by **November 27, 2006**.

HELP US HELP MILLIONS

National Institutes of Health
National Institute of Allergy and Infectious Diseases
ImmunoTechnology Section, Vaccine Research Center

Postdoctoral Researcher

The Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID and NIH bring together a diverse group of scientists with the goal of advancing vaccine-related research as well as initiating and advancing vaccine candidates through clinical trials. The ImmunoTechnology Section is a highly active and collaborative laboratory with several postdoctoral fellows, students, and biologists. For a detailed description of our laboratory's program, see selected publications (right) and http://www.vrc.nih.gov/VRC/labs_immunotechnology.htm.

Currently, we have a postdoctoral position available to study mucosal or central immune responses. We are using the nonhuman primate model (SIV infection) to define viral and cellular dynamics across all tissues and use state-of-the-art multicolor flow cytometers as well as cellular and molecular technologies uniquely available at the VRC and the NIH.

We are seeking a highly motivated and creative individual, with a Ph.D. or M.D. and experience in cellular or molecular immunology, to define and head a unique research program within the laboratory. Candidates with any level of training are encouraged to apply. Interested candidates should send a copy of their CV, and contact information for three references to:

Mario Roederer
VRC, NIAID, NIH
40 Convent Dr., Room 5509
Bethesda, MD 20892-3015
301-594-8491; FAX 301-480-2651
Email: Roederer@nih.gov

Selected references:

Mattapallil, J. J. et al. Massive infection and loss of memory CD4 T cells in multiple tissues during acute SIV infection. **Nature** 434, 1093-1097 (2005).
Mattapallil, J. J., et al. Vaccination preserves CD4 memory T cells during acute simian immunodeficiency virus challenge. **Journal of Experimental Medicine**, 203, 1533-41 (2006).
Chattopadhyay, P. K., et al. Quantum dot semiconductor nanocrystals for immunophenotyping by polychromatic flow cytometry. **Nature Medicine**, 12, 972-7 (2006).
Perfetto, S. P. et al. 17-Color Flow Cytometry: Unraveling the Immune System. **Nat Rev Immunol** 4, 648-655 (2004)

DALE AND BETTY BUMPERS
VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services
Vaccines for Life™

NIDDK

Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK POSTDOCTORAL POSITIONS within the Molecular and Clinical Hematology Branch are available to study hematopoiesis and hemoglobin switching. Current projects include studies of the molecular basis of lineage-specific differentiation of hematopoietic stem cells and the development of therapies for hemoglobinopathies and other genetic blood disorders. A strong background in molecular biology, cell biology and/or signal transduction is required. Opportunities exists to develop relevant clinical or translational projects. Salary and benefits will be commensurate with experience of the applicant. Interested candidates with an M.D. and/or Ph.D., and less than five years of postdoctoral experience should send a CV, bibliography, and names of three references to: **Griffin P. Rodgers, M.D. at (gr5n@nih.gov) or: Molecular and Clinical Hematology Branch, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 10 Center Drive, Building 10, Room 9N-119, Bethesda MD 20814**.

NIDDK

POSTDOCTORAL FELLOWSHIP in Molecular Genetics at the Department of Health and Human Services (DHHS), National Institutes of Health (NIH), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in Phoenix, Arizona. We are working to identify and characterize novel genes that cause type 2 diabetes and obesity in humans. Applicants must have a PhD. or M.D. degree obtained within the past 5 years, with research experience in molecular biology. Please send curriculum vitae to **Leslie Baier, Ph.D. 445 North 5th Street, Suite 210, National Institutes of Health, Phoenix, AZ 85004. email: lbaier@phx.niddk.nih.gov**

WWW.NIH.GOV

National Cancer Institute

Fellowships in Cancer Epidemiology and Genetics

Division of Cancer Epidemiology and Genetics

The Division of Cancer Epidemiology and Genetics (DCEG) of the National Cancer Institute conducts a national and international program of population- and family-based studies to elucidate the environmental and genetic determinants of cancer. DCEG is an intramural research unit within the National Institutes of Health, located in a suburb of Washington, D.C. DCEG is staffed by epidemiologists, geneticists, biostatisticians, and others who are committed to excellence in epidemiologic research and to training the next generation of scientists.

Research areas include:

- biostatistics and methodology
- cancer health disparities
- clinical genetics
- descriptive epidemiology
- diet and nutrition
- hormones
- host and endogenous factors
- environmental and lifestyle factors
- exposure assessment methods
- genetic and familial susceptibility
- gene-environment interactions
- infectious agents
- medications and medical histories
- molecular epidemiology
- multiple primary cancers
- occupational exposures
- quantitative risk assessment
- radiation

Fellowships

Fellows design, carry out, analyze, and publish research studies related to the etiology of cancer in human populations, and gain experience with interdisciplinary, interagency and multicenter collaborations.

Postdoctoral Fellowships

Fellowship training is up to five years under the supervision of DCEG scientists.

Eligibility Requirements

Applicants must:

- have an M.D. or doctoral degree in epidemiology, biostatistics, genetics, or other related research fields, or be pursuing a degree in these areas.
- be a U.S. citizen, resident alien, or foreign national eligible for a training visa.

Predoctoral Fellowships

Fellowships up to three years are offered to doctoral students for dissertation research and to master's level graduates. Applicants may be U.S. citizens, resident aliens, or those eligible for a training visa.

Application

Fellowship applications are accepted on an ongoing basis. Submit all application materials online at: ***www.dceg.cancer.gov*** under "Fellowships."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Positions @ NIH

The National Institutes of Health

Department of Health and Human Services
National Institutes of Health
Clinical Center

Tenure-track Physician
Clinical Center/Nuclear Medicine Department

This position is located in The Warren G. Magnuson Clinical Center, Nuclear Medicine Department (NMD).

We are seeking a research-oriented physician for a possible tenure-track position. An M.D. or M.D. /PhD with U.S. Nuclear Medicine Board certification and CT training is needed to provide diagnostic and therapeutic nuclear medicine procedures as well as to participate in clinical research protocols of the NIH Intramural Program. U.S. citizenship or permanent residency status is required.

Please submit your curriculum vitae, bibliography, and a letter describing your clinical, research, and management experience to: **Mrs. Veronica Olaaje, HR Specialist, DHHS, NIH, OD/CSD-E, 2115 E. Jefferson Street, Rm. 2B209 MSC-8503, Bethesda, MD 20892-8503. Phone: 301-435-4748. Email: volaaje@mail.nih.gov**.

Salary is commensurate with experience. This appointment offers a full benefits package (including retirement, health, life and long term care insurance, Thrift Savings Plan participation, etc.). Application packages should be submitted as early as possible, but no later than **December 31, 2006**.

Selection for this position will be based solely on merit, without discrimination for non-merit reasons such as race, color, religion, sex, national origin, politics, marital status, sexual orientation, physical or mental handicap, age or membership or non-membership in an employee organization.

Staff Scientist Position

The National Institute of Allergy and Infectious Diseases, a major research component of the NIH and the Department of Health and Human Services, is recruiting a Staff Scientist. The position will be available in the Respiratory Viruses Section of the Laboratory of Infectious Diseases, and scientists with a M.D., D.V.M, or Ph.D. are eligible. The research activity involves (1) examination of the pathogenesis of pandemic and potential pandemic strains of influenza and their evaluation in vitro and in experimental animals; (2) influenza viral genomics, and examination of viral evolution in fitness and host adaptation; and (3) the development of influenza clinical trials in humans. This full-time research position offers a unique opportunity to work on investigations that range from basic molecular biology to clinical research. Staff Scientist applicants should have at least six years of laboratory work experience in molecular and classical virology research; the salary range is $73,178 - $165,195. Preference will be given to candidates who have experience working with avian influenza viruses and those with BSL3 experience. Applicants should submit their curriculum vitae, a letter of research interests, and names and addresses of three references to:**Jeffery K. Taubenberger, MD, PhD, Attn: D. Kyle, NIAID, NIH, Bldg 50 Room 6234, MSC 8007, 50 South Drive, Bethesda, MD 20892-8007, FAX: (301) 496-8312, email: dkyle@niaid.nih.gov**

Review of applicants will begin on **October 30, 2006** and continue until a successful candidate is identified.

Postdoctoral Research Opportunities

Our goals are to investigate the dynamic interplay between signals from the extracellular environment and transcription by RNA polymerase II and to probe how chromatin structure and epigenetics influence gene activity. Although it has been known for many years that the compaction of DNA into chromatin can occlude protein binding sites and gene promoters, the ways in which the cellular machinery manipulates chromatin structure to influence gene expression remain poorly understood. Understanding the transcriptional responses to specific stimuli is crucial for a full appreciation of many biological and pathological events involving gene-environment interactions. Primary aims of our research are to elucidate the regulation of transcription elongation and to address how histone modifications and nucleosome remodeling affect Polymerase II movement through a gene. We are undertaking a variety of approaches to identify and characterize proteins that regulate transcription elongation and chromatin structure, combining in vivo RNAi, Microarray expression and ChIP-on-chip location analysis with in vitro biochemical and biophysical assays (e.g. Adelman, et al., PNAS, 2002; Mol. Cell, 2004; Mol. Cell, 2005; Mol. Cell Biol. 2006). These studies also take advantage of the availability of cutting-edge protein expression, structural biology and mass spectrometry facilities at the NIEHS, as well as the novel, single-molecule biophysical techniques that are being developed in our laboratory. Applicants must possess a Ph.D. degree in Biochemistry, Genetics or a related field and have less than three years of postdoctoral experience. Salary will be commensurate with experience. Candidates with experience in Drosophila or mouse models are especially encouraged to apply. Applications should be received no later than November 20, 2006. For consideration, send cover letter, curriculum vitae including list of publications, and the names/phone numbers/email addresses of three people who could provide letters of reference to: Karen Adelman, Laboratory of Molecular Carcinogenesis, NIEHS/ NIH, Room D454A, Mail Drop D4-02, 111 Alexander Drive, Research Triangle Park, NC 27709, FAX: 919-541-0146, Email: adelmank@niehs.nih.gov, http://dir.niehs.nih.gov/dirlmc/transcript.htm

Department of Health and Human Services
National Institutes of Health
Tenure-Track Position

The Division of Intramural Research, National Institute on Deafness and Other Communication Disorders (NIDCD), located in Bethesda, MD, is seeking a tenure-track scientist to establish an independent research program to study molecular and/or cellular mechanisms of hearing and balance. We welcome applications from candidates with a wide range of expertise. Preference will be given to candidates whose experimental approaches complement those of our existing strong programs in the genetics, development and cell biology of hearing. The successful candidate will join a dynamic group of scientists in a growing intramural program that is at the forefront of research on communication disorders.

The NIDCD offers an exceptional working environment including well-equipped research laboratories and numerous opportunities for collaboration. Candidates for this position must possess a Ph.D. and/or M.D., post-doctoral experience, and an outstanding publication record. Salary is commensurate with education and experience.

Please submit a curriculum vitae including bibliography, three reprints of recent relevant publications, statement of research interests, an outline of your proposed research, and the names and addresses of three references to: **Ms. Trudy Joiner, Office of the Scientific Director, NIDCD, 5 Research Court, Room 2B28, Rockville, MD 20850 (joinert@nidcd.nih.gov)**. Applications will be accepted until **December 15, 2006**.

Department of Health and Human Services
National Institutes of Health
National Cancer Institute

Tenure-Track Principal Investigator, Laboratory of Biochemistry and Molecular Biology
Center for Cancer Research, NCI

The Center for Cancer Research (CCR), National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services (DHHS) is accepting applications for a Tenure-Track Investigator in the Laboratory of Biochemistry and Molecular Biology (LBMB). The CCR's mission is to reduce the burden of cancer through exploration, discovery, and translation. As part of this mission, the LBMB investigates basic cellular processes, with an emphasis on the biology and biochemistry of chromosomes and the cell nucleus. LBMB fosters a highly interactive and collaborative environment that is supportive of junior investigators. Investigator research interests include:

Carl Wu—Chromatin remodeling, transcription, and functions of histone variants
Yawen Bai—mechanisms of protein folding and protein dynamics
Dhruba Chattoraj--maintenance of multiple chromosomes in *Vibrio cholerae*
Shiv Grewal—RNAi and higher-order chromatin assembly in *S. pombe*
Michael Lichten—meiotic recombination and chromosome structure in *S. cerevisiae*
Bruce Paterson—myogenesis and regulatory RNA pathways in Drosophila
Yikang Rong—DNA repair and telomere maintenance in Drosophila

Candidates should have a Ph.D. or M.D. degree with proven ability to conduct innovative research in the broad areas of genome expression, transmission, and stability. The successful candidate will perform independent research funded by the NIH Intramural Research Program as a member of the LBMB, and will also participate in the CCR Center of Excellence in Chromosome Biology (CECB). More information can be obtained at the following the websites:
LBMB--http://ccr.cancer.gov/labs/lab.asp?labid=783 , CECB--http://ccr.nci.nih.gov/initiatives/CECB/.
Send C.V., statement of research plans, and 3 letters of recommendation by **December 4, 2006** to: **NCILBMBsearch@mail.nih.gov or to Zoraida Villadiego, NIH, Bldg 37 Rm 6106C, MSC 4260, Bethesda, MD 20892**. Electronic submissions are encouraged.

HIV and AIDS Malignancy Branch
Center for Cancer Research

Tenured/Tenure Track Position
Translational Researcher in Viral Oncogenesis

The HIV and AIDS Malignancy Branch (HAMB), NCI, is searching for a tenure-track or tenured investigator in the field of viral oncogenesis. It is anticipated that the investigator will establish an independent research program targeted to the study of the treatment, pathogenesis, and/or prevention of viral-induced tumors, especially those associated with AIDS. The research program should be translational in focus and be able to interface with a strong existing clinical research program in AIDS-related tumors. HAMB is located on the Bethesda campus of the NIH (http://ccr.cancer.gov/labs/lab.asp?labid=63). Current areas of research in HAMB focus on Kaposi's sarcoma-associated herpesvirus (KSHV /HHV -8)-associated tumors, the molecular biology of human papillomavirus (HPV), and the development of novel therapeutic interventions for HIV infection. Candidates for the position should have an M.D./Ph.D., Ph.D., or M.D. and strong research credentials. Applicants for this position should submit a curriculum vitae including bibliography, a statement of research interests, a two-page outline of the proposed research program, and the names of three references to **Chairman, Search Committee, HAMB, NCI, Attention Jan Huque, Building 10, Rm.10S255, 10 Center Drive, M.S.C. 1868, Bethesda, MD 20892-1868 no later than December 21, 2006**. You may also e-mail your application to: **huquej@mail.nih.gov (Jan Huque, 301-435-4627)**.

Department of Health and Human Services
National Institutes of Health
National Cancer Institutes

Tenure-Track Principal Investigator, Laboratory of Cellular Oncology and Center for Cancer Research, NCI.

The Laboratory of Cellular Oncology (LCO), Center for Cancer Research, of the National Institutes of Health, invites applications for a tenure track or tenure eligible principal investigator position in the area of research on papillomavirus biology, including vaccines. The LCO, which occupies recently renovated laboratory space, fosters an interactive research environment and the use of diverse experimental approaches and model systems. Applicants should have a Ph.D. and/or M.D. degree, a strong publication record, and demonstrated potential for imaginative research. Salary will be commensurate with education and experience. A one- or two-page statement of research interests and goals should be submitted in addition to three letters of recommendation and a curriculum vitae to: **Theresa Jones, Laboratory of Cellular Oncology, National Cancer Institute, NIH, Building 37, Room 4106, Convent Drive MSC 4263, Bethesda, MD 20892-4263; phone: 301-496-9513; fax: 301-480-5322; email: jonest@DC37A.nci.nih.gov**. Candidates must be U.S. citizens or permanent residents.

Applications must be received by 1**1/22/06**. The National Cancer Institute is an Equal Opportunity Employer. Selection for this position will be based solely on merit, with no discrimination for non-merit reasons such as race, color, religion, gender, national origin, politics, marital status, physical or mental disability, age, sexual orientations, or membership or non-membership in an employee organization.

UNIVERSITY OF CALGARY

THE HEART AND STROKE FOUNDATION OF ALBERTA, NWT & NUNAVUT CHAIR IN STROKE RESEARCH

The **Faculty of Medicine** invites applications for a full-time academic position at The Heart and Stroke Foundation of Alberta, NWT & Nunavut Chair in Stroke Research. The Chair holder will be appointed in the Department of Clinical Neurosciences and will become a full member of the Hotchkiss Brain Institute. The successful candidate will be a clinical or basic scientist with a distinguished reputation and proven leadership in research and education in the field. Eligibility for licensure in the Province of Alberta and privileges within the Calgary Health Region are required if the selected individual will provide patient care.

The University of Calgary and Calgary Health Region have developed a reputation for excellence in stroke research and its translation into superior patient care, supported, in part, by outstanding human and animal imaging facilities and expertise in neuroscience and vascular biology. The Chair holder will provide leadership in the development of translational stroke research in Southern Alberta, and will support the establishment of research and education collaborations and linkages provincially, nationally and internationally.

The successful candidate's research interests may fall within any of the four CIHR pillars; basic biomedical, clinical, health services, and/or population health research. As a research and education leader, the Chair holder will help attract and support outstanding trainees and scholars in the field of stroke research. The successful candidate will also establish links with key community-based groups, such as the Heart and Stroke Foundation of Alberta, NWT & Nunavut.

The selected candidate will be expected to compete for salary support and establishment funding from the Alberta Heritage Foundation for Medical Research. Start-up funds will also be available through the Chair.

The Faculty of Medicine is a leader in health research with an international reputation for excellence and innovation. The Faculty of Medicine's research culture and infrastructure facilitate multidisciplinary studies using state-of-the-art investigative tools. Calgary is a vibrant, multicultural city of a million people. There are extensive cultural and recreational opportunities within the city and the nearby Rocky Mountains.

The Department of Clinical Neurosciences and the Hotchkiss Brain Institute are working together to enable integrated, outcome-focused research and education activities. One of the eight Hotchkiss Brain Institute research programs is focused on translational stroke research and education activities. See the website www.hbi.ucalgary.ca for more information on the institute.

Please submit a curriculum vitae, a statement of research interests and goals, and the names of three referees by **December 31, 2006,** to:

Dr. P.A. Sokol, Vice-Dean
Faculty of Medicine
3330 Hospital Dr. N.W.
Calgary, Alberta, Canada T2N 4N1

In accordance with Canadian immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada. The University of Calgary respects, appreciates and encourages diversity.

www.ucalgary.ca

TENURE-TRACK FACULTY POSITION

Thomas Jefferson University

The Department of Pathology, Anatomy and Cell Biology invites applications for a research-oriented, tenure-track position at the **Assistant or Associate Professor** level in the general areas of Infectious Diseases, Immunobiology, Autoimmunity, Host Defenses, and/or Inflammatory Diseases. Candidates should have research programs in mechanisms of immune-mediated diseases or development of immune-based diagnostics and therapeutics that will complement ongoing faculty research in HIV, hepatitis, and malaria. Candidates must have a PhD or MD degree and a commitment to teaching in Departmental education programs. Applicants should have a strong independent research program or a demonstrated potential for independence. Candidates for Associate Professor must have a strong record of extramural funding.

Interested candidates are invited to submit curriculum vitae and names of three academic references to:

Sue Menko, PhD, sue.menko@jefferson.edu, Chair, Search Committee, Professor, Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, JAH 571, 1020 Locust Street, Philadelphia, PA 19107. EOE

faculty position

Gladstone Institute of Virology and Immunology
University of California, San Francisco

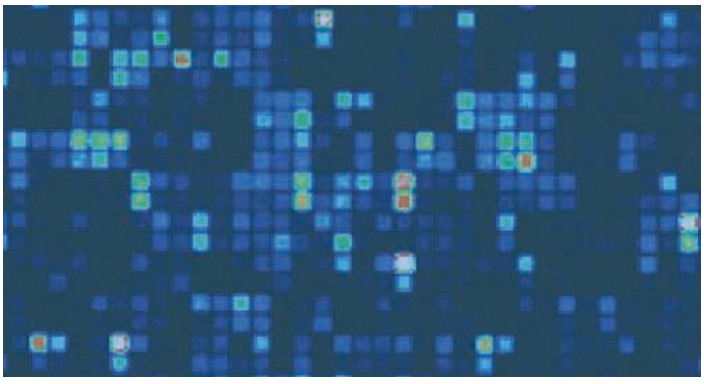
PhD and/or MD scientists with demonstrated research interests and accomplishments in the field of HIV virology or immunology or closely related disciplines like HCV virology, coupled with a strong record of scientific achievement, are invited to apply for a faculty position at the Assistant/Associate/Full Investigator level within the Institute, and a comparable Assistant/Associate/Full Professorship at UCSF. A successful candidate will receive ongoing salary and research support from the Gladstone Institutes and laboratory and office space in the new Gladstone research building at the Mission Bay campus of UCSF. Please submit a *curriculum vitae*, a short description of future research plans, and the names of three references, by December 15, to the Chair of the Faculty Search Committee at:

givisearch@gladstone.ucsf.edu

Gladstone Institute of Virology and Immunology
1650 Owens Street, San Francisco, CA 94158-2261
On the internet: http://www.gladstone.ucsf.edu

GLADSTONE

The Gladstone Institutes and UCSF are affirmative action/equal opportunity employers Gladstone and the University undertake affirmative action to assure equal employment opportunity for underutilized minorities and women, for persons with disabilities, and for Vietnam-era veterans and special disabled veterans. We seek candidates whose experience, teaching, research, or community service has prepared them to contribute to our commitment to diversity and excellence.



Michael, Rituxan® Patient

BECAUSE

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Please take this opportunity to learn about Genentech, where we believe that our employees are our most important asset.

Genentech is dedicated to fostering an environment that is inclusive and encourages diversity of thought, style, skills and perspective. To learn more about these opportunities, please visit **www.gene.com/careers** and reference the Req. #. Please use **"Ad - Science"** when a "source" is requested. Genentech is an equal opportunity employer.

We are currently seeking Senior Scientists and Scientists in our Departments of Immunology, Immunology Diagnostics and Microbial Pathogenesis in our South San Francisco headquarters.

All positions require a PhD, MD or PhD/MD.

Senior Scientist – Immunology, Req. #1000012848
Lead a group of independent Scientists, Research Associates and Postdoctoral Fellows and build a program in tumor immunology and/or autoimmunity. This program will apply human and murine model systems to design and develop therapeutic strategies aimed at regulating the immune system against tumor or self-antigens.

Scientist – Immunology, Req. #1000012849, #1000012850
Develop laboratories aimed at discovering novel immunobiology and translating discoveries into innovative therapeutics. Areas of interest include dendritic cell biology and tumor immunology. Candidates must bring forward novel drug candidates for the development pipeline and publish work in top-tier journals.

Scientist – Immunology Diagnostics, Req. #1000014930
Discover novel immunobiology and translate discoveries into innovative therapeutics and biomarkers. Areas of interest include B-cell immunology and autoimmunity. Candidates should be committed to understanding human disease pathogenesis, mechanisms of therapeutics and identification of markers that may predict clinical efficacy.

Senior Scientist – Microbial Pathogenesis, Req. #1000015208
Scientist – Microbial Pathogenesis, Req. #1000015207
Lead and build research programs in the area of microbial pathogenesis, focusing on understanding the molecular mechanisms by which microbes invade the human host, host-pathogen relationships and drug discovery. Experience in bacteriology and/or virology is required.

Senior Scientists should have an established reputation in leading a research laboratory in academia or industry, proven sustained record of outstanding research performance and major scientific accomplishments. **Scientists** should have postdoctoral experience with an outstanding record of scientific accomplishment in modern human and/or murine immunology as evidenced by the quality of publications.

Genentech was named #1 on Science Magazine's 2006 "Top Employer" list.

Science 2006 TOP EMPLOYER

Genentech
IN BUSINESS FOR LIFE

UNIVERSITY OF CALIFORNIA, RIVERSIDE

Assistant Professor, Molecular Basis of Chemoreception and/or Behavior in Insects, starting July 1, 2007. Position is tenure track, 11 months/year, 25% teaching, 75% research. Appointment level and salary commensurate with experience. Ph.D. with extensive training in using molecular biology techniques to investigate chemoreception and/or behavior in insects is required. Postdoctoral experience an asset. The appointee will develop a strong basic and applied research program, participate in graduate and undergraduate teaching in Entomology and interdepartmental programs, and supervise graduate students. Applicants should send CV, statement of research interests, reprints and manuscripts in press, and arrange to have four letters of reference sent to: **Jocelyn Millar, Search Committee Chair, Department of Entomology, University of California, Riverside, CA, 92521, USA; e-mail: Jocelyn.millar@ucr.edu, phone (951) 827-5821, FAX (951) 827-3086**. Applications may be submitted electronically or by mail. Letters of reference may be sent by email, with signed hard copies following. Applications, including letters, should be received by **December 31, 2006**, but position will remain open until filled. Further information about the Entomology Department and the position can be found at **http://www.entomology.ucr.edu**. Information on UC Riverside's numerous Interdepartmental Programs can be found at **http://www.ucr.edu/academic.html**.

Assistant Professor, Molecular Basis of Plant Pathogen Interactions with Insects or Other Arthropod Vectors, available July 1, 2007. Successful candidate will hold a faculty position in an academic department appropriate for her/his discipline, and will be affiliated with our Institute for Integrative Genome Biology. Individuals must work at the forefront of research on vectors of plant pathogens, utilizing multidisciplinary molecular approaches including genomics, proteomics, and bioinformatics to understand mechanisms by which insects and other arthropods acquire and transmit pathogens, with the long-term goal of solving problems caused by plant diseases. Successful candidate will be expected to establish an independent, innovative, and vigorous research program, have a strong commitment to excellence in undergraduate and graduate teaching, and participate in departmental and interdepartmental graduate programs. Position is an 11-month appointment in the Agricultural Experiment Station, 25% teaching, 75% research. Applicants must hold a Ph.D. in Entomology, Plant Pathology, Molecular Biology, Insect Physiology, Genetics, Cell Biology, or a related discipline. Postdoctoral experience using modern molecular and genomic techniques an asset, but not required. Review of applications will begin during January 2007, and continue until position is filled. Applicants should submit curriculum vitae and statement of research interests, and have three letters of recommendation sent to: **Professor Brian A. Federici, Chair, Plant Pathogen Vector Search Committee, Department of Entomology, 900 University Avenue, University of California, Riverside, CA 92521**.

The University of California is an Equal Opportunity/Affirmative Action Employer.

State University of New York
College of Environmental Science and Forestry

Tenure Track Position in Ecology
Adirondack Ecological Center

The State University of New York College of Environmental Science and Forestry in Syracuse invites applications for a Research Associate in Ecology at its Adirondack Ecological Center. A Ph.D. in ecology or related discipline is required. Qualified candidates must demonstrate a primary interest in forest ecosystems and sustainability. Preference will be given to candidates with a record of excellence in research and outreach, and who have strong quantitative skills including modeling, biometry, landscape ecology and spatial analysis. The successful candidate is expected to lead interdisciplinary investigations to understand the complex interactions among forest and human systems. Special attention is to be given to issues of sustainability in Adirondack Park and the Northern Forest, from local to landscape scales. Teaching will be an important secondary activity and will include on-site short-courses and distance-learning courses.

The Adirondack Ecological Center is located in the heart of Adirondack Park, a 6 million acre wilderness in northern New York. Its mission is to understand the Adirondack ecosystem through research. As the largest field station in the SUNY system, it has more than 50 ongoing research programs and a 75-year record of producing leaders in environmental sciences and natural resources management.

For details and application procedures, see **www.esf.edu/aec** or **www.esf.edu/hr/search**

SUNY-ESF is an Equal Opportunity/Affirmative Action employer.

National Health Research Institutes (NHRI)
Taiwan, R.O.C.
Director, Division of Molecular and Genomic Medicine

NHRI, a leading non-profit medical research organization in Taiwan, cordially invites senior scientists to apply for the Director of the Division of Molecular and Genomic Medicine. The Director will be responsible for the planning, developing, coordinating, and implementing of the Division's intramural research programs. The ideal candidate should hold either a Ph.D. or M.D. degree or both with a strong background in Molecular Biology or Genomic research.

Candidates should have senior level Cell and Molecular Biology research experience that demonstrates the ability and scientific status sufficient to advise the research staffs in the division. A proven track record of leadership in Genomic research is required, with emphasis on Cell Biology, Genetics, Molecular Biology and Biomedical Sciences. Candidates are also expected to be familiar with the scientific community in Taiwan and proficient in the Chinese language, and capable of working effectively in the research environment under current circumstances in Taiwan. Salary will be highly competitive with comparable positions in Taiwan.

Application should include:
(1) A letter of intent
(2) Curriculum vitae with publication list
(3) A copy each of five major recent publications
(4) Three to five Recommendation letters

Apply to: Kenneth Kun-Yu Wu, MD., PhD., President, NHRI
e-mail: **kkgo@nhri.org.tw**

Address: National Health Research Institutes, 35, Keyan Road, Zhunan Town, Miaoli County 350, Taiwan, R.O.C.

NHRI website: **http://www.nhri.org.tw**
Tel: 886-37-246166; Fax: 886-37-586401

Closing Date: December / 31 / 2006

IRD
Institut de recherche pour le développement

L'Institut de Recherche pour le Développement (IRD)

Director of the Centre of Research and Surveillance on Emerging Diseases in the Indian Ocean

New Joint Scientific Research Venture based in Saint Denis, Réunion

Duties and functions:
- coordination of scientific research and surveillance activities on emerging diseases in the Indian Ocean region.
- stimulation and setting-up of new research programmes in these fields.
- management of administrative and financial aspects of the centre.
- organization and leadership of a partnership network, at local and regional levels within the Indian Ocean Commission and also at international scale.

The post requires high-level education and training and substantial experience in the field of research in epidemiology, infectious disease prevention and treatment and other health-related disciplines. The successful candidate will have a good knowledge of multidisciplinary research on emerging diseases. You must have gained international recognition for your research activities, organization and leadership and have considerable team management experience.

You must be bilingual French/English.
Last date for applications: 1 December 2006.
Call for applications in detail on www.ird.fr
Post location: Saint Denis, Réunion.
Type of contract: Secondment, guest research director contract, or contract and isolated post allowance.
Qualifications: Doctorate and HDR (Director of research diploma) or equivalent level.

CV, covering letter and written account of publications and work conducted to be sent to:
- candidat@paris.ird.fr, reference: poste Directeur Réunion

or

- Directeur des Personnels, Institut de Recherche pour le Développement, 213 rue La Fayette, 75480 Paris cedex 10, France

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Join a Network of Nearly 2,000 Fellows.
AAAS Fellows benefit from a growing and diverse network of colleagues. Applicants must hold a PhD or equivalent doctoral-level degree in any physical, biological, medical/health, or social science, or any engineering discipline. Individuals with a master's degree in engineering and three years of post-degree professional experience also may apply. Federal employees are not eligible and U.S. citizenship is required.

Apply Now!
The application deadline for the 2007-2008 Fellowships is 20 December 2006. Fellowships are awarded in the spring and begin in September. Stipends range from $67,000 to $87,000, depending on experience.
To apply: fellowships.aaas.org

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Christina Kakoyannis, PhD

Forest Resources,
Oregon State University.

2005-2007 AAAS Fellow at the U.S. Environmental Protection Agency in the Office of Environmental Policy Innovation, Evaluation Support Division.

AAAS
ADVANCING SCIENCE, SERVING SOCIETY

Associate Director
Josephine Ford Cancer Center
Henry Ford Health System

Henry Ford Health System invites applications or nominations for the position of Associate Director of the Josephine Ford Cancer Center (JFCC). Candidates must have a Ph.D. and/or M.D., and should be nationally recognized experts in cancer biology. They must have a proven record of establishing and managing research programs that attract Federal funding (NIH RO1 or PO1). Candidates with current funding from NIH or other Federal agencies are preferred. Research fields of interest may include, but is not limited to, mechanical studies such as signaling pathways controlling cancer cell proliferation, viability, invasion, or metastasis in cancer prevention, control or treatment.

Henry Ford Health System has an exciting and highly productive team of over 30 cancer researchers with extramural funding of $13 million/year. The successful candidate will be responsible for developing a comprehensive strategic plan that fosters scientific interaction between Henry Ford Hospital researchers currently working in various cancer fields, including blood, brain, breast, head and neck, kidney, prostate, and skin. Associate Director, working closely with the Director, will determine allocation of JFCC resources to build research infrastructure that is conducive to the advancement of inter-disciplinary research programs. These interactive research programs are expected to enhance extramural funding opportunities for researchers of the JFCC, and lead to the establishment of the JFCC as an NCI-designated Cancer Center.

A generous package of research and office space, startup funds, and a Professor level salary commensurate with qualification and experience will be offered.

Interested applicants should submit an outline of current and future research interests, funding history, a CV, and the names and addresses of five references to:

G. Prem Veer Reddy, Ph.D.
Chairman, JFCC Associate Director Search Committee
Henry Ford Health System
One Ford Place, 2D
Detroit, MI 48202
Phone: (313) 874-5991
Fax: (313) 874-4324
Email: preddy1@hfhs.org

For fullest consideration, submit applications by **December 15, 2006** with anticipated start date in Spring 2007.

AA/EEO

The
Institute of Microbial Technology, Chandigarh (CSIR, India)

invites applications for filling up to sixteen available 'scientist' positions at different levels/ grades from persons wishing to carry out R&D at IMTECH in various fundamental and applied research areas of modern biology and biotechnology, such as infectious diseases and immune mechanisms, protein science & engineering, systems biology, metabolic engineering, fermentation and downstream processing, bioinformatics, microbial physiology and genetics etc.

Details concerning the institute, salaries and allowances at the available positions, and application procedure may be found at **www.imtech.res.in**

Professor and Chair

The University of Nebraska-Lincoln (UNL) invites applications and nominations for Professor and Chair of the Department of Chemistry. We are seeking candidates with an outstanding research program, a history of strong external funding, demonstrable leadership ability, excellent interpersonal skills, and a vision for enhancing the research and educational programs of the department. Candidates should have a Ph.D. in chemistry or a closely related field. The position may be associated with an endowed professorship.

The Department has a long tradition of excellence in both teaching and research. We are an ACS-certified program offering both B.S. and B.A. Chemistry degrees. Departmental courses also support campus liberal arts requirements as well the degree programs of a number of other majors. The only Ph.D.-granting chemistry program in the state and one of the premier research units within the University, the Department is housed in Hamilton Hall, an eight-story 200,000 sq. ft facility dedicated to research and teaching in chemistry. Nearly half of departmental research space has been recently renovated with support from two NIH infrastructure grants. Research programs span traditional and interdisciplinary areas of chemistry, including materials science, biotechnology, structural biology/proteomics, water science, environmental toxicology, and cancer research. The department anticipates a number of faculty hires at all levels as part of strategic campus initiatives in several interdisciplinary areas. UNL is also recruiting a new chair for the Department of Biochemistry, providing a unique opportunity for the successful candidate to collaborate on joint programs. The Department has strong support from alumni and is assisted by an active Industrial Advisory Board. Additional information about the department can be found at **http://www.chem.unl.edu**.

To be considered for the position, applicants must complete the Faculty/Academic Administrative Information Form at **http://employment.unl.edu, requisition 060879**. Then under separate cover send a cover letter, a curriculum vitae with a full list of publications, a summary of past, current and pending research support, the names of three references, and a brief statement of research, educational, service, and administrative interests. Nominations and applications should be sent to: **Chemistry Chair Search Committee, c/o Dean Richard Hoffmann, College of Arts and Sciences, 1223 Oldfather Hall, University of Nebraska-Lincoln, Lincoln, NE 68588-0312 (e-mail: chemistrychairsearch@unl.edu)**. Review of applications will begin **November 30, 2006** and will continue until the position is filled.

The University of Nebraska is committed to a pluralistic campus community through Affirmative Action and Equal Opportunity and is responsive to the needs of dual career couples. We assure reasonable accommodation under the Americans with Disabilities Act; contact the search committee (402 472-6262 or chemistrychairsearch@unl.edu) for assistance.

Brown University
Center for Computational Molecular Biology
Faculty Position

Brown University seeks highly qualified candidates for one open rank, tenure-track or tenured faculty position with a preference for assistant professor in the Center for Computational Molecular Biology (CCMB). The growing CCMB currently has four full-time faculty members, two in Computer Science, one in Applied Mathematics and one in Biology. Candidates are sought in all areas of computational biology and bioinformatics, particularly those who specialize in research areas complementary to and synergistic with those of current faculty. The research areas of the current Center faculty are: algorithmic methods and statistical inference in genomics, comparative genomics and evolution, gene regulatory networks, regulatory genomics, mathematical models of genetic variation, and cancer genomics.

The successful applicant will be expected to have a demonstrated potential for excellence in research and have outstanding teaching skills. Junior faculty applicants should show the potential to establish an externally funded research program; senior faculty applicants should have established such a program. The appointee will participate in the continuing development of Brown's established undergraduate Computational Biology curriculum and a newer graduate curriculum built upon the foundation of Brown's widely recognized record of teaching innovation and academic excellence. The appointee will have the opportunity to participate in several interdisciplinary projects, including collaborations with faculty in the Center for Genomics and Proteomics, the Center for Cardiovascular Research and other multidisciplinary programs at Brown and affiliated hospitals. The appointment will be in one of the following top-ranked departments: Division of Applied Mathematics, Department of Computer Science, or Division of Biology and Medicine.

Applicants should submit curriculum vitae, representative preprints or reprints, and their research and teaching plans with emphasis on their interdisciplinary expertise. Additionally, candidates for Assistant Professor should arrange to have at least three letters of recommendation sent directly to the contact address. Candidates for Associate or Full Professor should provide names and contact information for at least five references, who will be contacted for letters of recommendation by the search committee at an appropriate time. All applications will be treated confidentially. Application review will commence on **December 18, 2006** and continue until the position is filled. All documents should be sent electronically in PDF to: **ccmbfs@cs.brown.edu**. In addition, please send the cover letter and letters of recommendation to: **Sorin Istrail ~ Chair, CCMB Search Committee, Center for Computational Molecular Biology, Brown University, Box 1910, 115 Waterman Street, Providence, RI 02912**. For further information, see **http://www.brown.edu/Research/CCMB**.

Brown University is an Affirmative Action/Equal Opportunity Employer.
Women and minorities are encouraged to apply.

Tenure-track and tenured faculty position openings at the Department of Physics of Sungkyunkwan University, Republic of Korea

We are inviting applications from outstanding candidates for assistant,associate, and full professor positions in all fields of physics research. The candidate must have a Ph.D. in Physics, with several years of post-doctoral or equivalent research experience, and have a proven track record of excellent research accomplishments. We are seeking energetic faculty members with strong potential to become leaders in their respective fields of research. The salary will be commensurate with experience. Being acknowledged for excellent research accomplishments, our department is one of only seven physics departments in Korea to have been awarded the Brain Korea 21 (BK21) grant for the next seven years. For a detailed description of the department faculty members and activities, please visit our web site at **http://physics.skku.ac.kr**

Please send a cover letter, curriculum vitae, and a list of publications to **physics@physics.skku.ac.kr**. The cover letter should indicate for which position the candidate is applying and the field of research. We ask that the candidate also provide us with a list of three references, but, at this point, we ask that the recommendation letters not be sent to the department. An application through e-mail is preferred, but the one through FAX or postal mail is also accepted. Deadline for application is November 30th 2006.

Prof. Young Hee Lee, Head of BK21 Physics, Research Division, Department of Physics, Sungkyunkwan University, Jangan-gu Chunchun-dong 300, Suwon 440-746, Republic of Korea.

ASSUMPTION COLLEGE
IMMUNOLOGY

Assumption College, a liberal arts and professional studies college, invites applicants for a tenure-track position at the **ASSISTANT PROFESSOR** rank, starting August 2007. Teaching duties include immunology, upper-level courses in vertebrate biology, and shared responsibility for introductory courses. Our new science building includes dedicated space for student-faculty research. Ph.D. and a commitment to undergraduate teaching and research required. Post-doctoral experience preferred. Candidates must understand and support the Catholic liberal arts mission of the College.

Send curriculum vitae, statements of teaching philosophy and research interests, graduate and undergraduate transcripts, and three letters of recommendation to: **Kimberly Schandel, (kschande@assumption.edu), Department of Natural Sciences, Assumption College, 500 Salisbury Street, Worcester, MA 01609-1296** by **December 1, 2006**.

Assumption College is an Affirmative Action Employer and encourages applications from candidates of diverse cultural backgrounds.

www.assumption.edu/programs/NatSc

ST. MARY'S UNIVERSITY

Fostering
Academic Excellence
And Spiritual Growth

ASSISTANT PROFESSOR BIOLOGIST

St. Mary's University of San Antonio, a private, Catholic university invites applications for a full-time tenure track faculty position in the Department of Biological Sciences beginning August 2007. We are seeking a candidate with expertise in an area of biology that will complement the current strengths of the department. Candidates with expertise in all fields of biology are encouraged to apply, especially those with training and expertise in the areas of molecular biology and evolutionary biology.

The primary responsibilities of this position will be teaching two courses with associated laboratory per semester. These courses will include introductory biology as well as courses to be developed by the candidate in his/her area of specialty. While teaching is the primary function of the position, research, especially involving undergraduates, is expected of the successful candidate. The presence of an active biomedical research community in the San Antonio area provides the opportunity to establish collaborative research projects in many fields. A Ph.D. in Biology or a related discipline is required and postdoctoral experience is preferred.

Founded in 1852 and operated by the Society of Mary, St. Mary's University is a Hispanic Serving Institution with a proven history of preparing undergraduate science students for careers in health professions and research. For more information visit the university web site at **www.stmarytx.edu** or contact the chair at **cnolan@stmarytx.edu** or 210-436-3241. Salary is commensurate with experience and is accompanied by a strong benefits package.

All qualified applicants are welcome; minorities and women are encouraged to apply. Applicants should submit a letter of application detailing interest in the position and a description of teaching and professional development goals, a curriculum vita, copies of graduate transcripts, the e-mail addresses and telephone numbers of references, and have three letters of recommendation sent to:

Dr. Colleen J. Nolan, Chair
Department of Biological Sciences
St. Mary's University
San Antonio, TX 78228-8607

Electronic submission of applications is encouraged, however, incomplete applications may not be considered. Review of applications will begin November 25, 2006 and will continue until a suitable candidate is identified. St. Mary's University is an Equal Opportunity Employer.

Professorial Appointment in Immunology/Allergy

MRC & Asthma UK Centre in Allergic Mechanisms of Asthma
Randall Division of Cell & Molecular Biophysics
KCL School of Biomedical and Health Sciences

Applications are invited for this non-clinical professorial post. The appointee will be based within the Randall Division of Cell & Molecular Biophysics, joining the Allergy and Asthma Research Group (BJ Sutton, HJ Gould and AJ Beavil), with joint membership of the Division of Asthma, Allergy and Lung Biology. The applicant will be a member of the newly established MRC & Asthma UK Centre in Allergic Mechanisms of Asthma (directed by Prof. Tak Lee) (www.asthma-allergy.ac.uk).

The Randall Division (www.kcl.ac.uk/schools/biohealth/research/randall/) offers a multidisciplinary research environment that encompasses molecular and cell biology (including live cell imaging), high-resolution optical microscopy (including a 4Pi microscope), structural biology (X-ray crystallography and NMR) and bioinformatics. The MRC & Asthma UK Centre brings together research groups at both King's College London and Imperial College with a common interest in Allergy and Asthma, providing common core facilities (including protein expression and animal airway measurement) and a network of clinical collaborations across a number of London hospitals that offers access to clinical facilities and materials.

We are seeking individuals with an internationally recognised track record of research achievement in any aspect of immunology that has relevance to the understanding of the molecular mechanisms of allergy and/or asthma. We will consider individuals with research interests that complement any of the research programmes of the Centre, namely: IgE structure, function and regulation; leukocyte trafficking, inflammation and airway structure; immunomodulation; infections. Applicants who have a previous competitive research programme in molecular immunology would have an advantage.

The salary will be on the Professorial (non-clinical, Band 1) salary scale.

For an informal discussion about the position, please contact Professor Brian Sutton, (Randall Division of Cell & Molecular Biophysics, King's College London, New Hunt's House, Guy's Campus, London SE1 1UL) on +44 (0) 20 7 848 6423 or email brian.sutton@kcl.ac.uk
For an application pack, please send an A4 SAE to Dipa Bhudia, Personnel Department, 4th Floor, Capital House, Weston Street, London SE1 3QD or email personnel-applications@kcl.ac.uk quoting reference number A5/MA/101/06.
Closing date for submission of completed application: 7 December 2006.

KING'S College LONDON

Equality of opportunity is College policy

University of London

Research Group Leaders

London Research Institute

Cancer Research UK is the largest independent cancer research organisation in Europe, conducting wide-ranging programmes in basic, applied and clinical research. The Cancer Research UK London Research Institute comprises laboratories at Lincoln's Inn Fields in central London, and at Clare Hall in Hertfordshire. The LRI is Cancer Research UK's largest research institute, housing almost 50 research groups, with an international staff working in laboratories featuring state-of-the-art scientific support facilities. Research at the Institute is core-funded through Cancer Research UK, including support for research fellows and graduate students, together with generous funding for laboratory equipment and consumables.

Research at LRI focusses on the analysis of fundamental processes in cell growth and transformation around two core themes of signal transduction processes and genomic integrity. Research groups at the institute study growth in cell size, mass, and shape, control of cell division cycle, and replication of the genome; how these processes are affected by environmental signals, tissue environment and physical stress; and how their disruption allows and promotes tumour development and spread.

In the 2007 recruitment round, we are seeking innovative scientists to run independent research programmes at the Institute's Lincoln's Inn Fields Laboratories, specialising in:

molecular and cellular approaches to address fundamental questions in

Immunology

including

tumor immunology; inflammation and innate immunity; immunosuppressive mechanisms; T cell tolerance; NK cell biology; imaging of immune cell interactions

(search coordinator: Caetano Reis e Sousa)

Appointments will be made at junior or senior level according to experience.

Junior appointments are for six years in the first instance with consideration for promotion to Senior Group leader in the fifth year.

For information about the London Research Institute, its staff and their research interests visit http://www.london-research-institute.co.uk/
Informal e-mail enquiries may be made to Dr Reis e Sousa at: caetano@cancer.org.uk

Applications should be submitted electronically to Dr Ava Yeo at the address below and must include:

1. Complete CV
2. Past and current research interests (approx 500 words)
3. Detailed future research proposals (approx 1000 words).

Three referees should be instructed to submit letters of recommendation when the application is submitted to:
Dr Ava Yeo, Director of Operations, London Research Institute, 44 Lincoln's Inn Fields, London WC2A 3PX, UK.

E-mail: ava.yeo@cancer.org.uk

Confidential Fax (references only): (44)-20-7269-3585

Applications should be received by December 16th 2006

CANCER RESEARCH UK
LONDON RESEARCH INSTITUTE
LINCOLN'S INN FIELDS
CLARE HALL

Charity no: 1089464

TENURE-TRACK FACULTY POSITION
Department of Surgery
The University of Chicago

The Department of Surgery at The University of Chicago seeks applicants for a faculty position at the rank of ASSISTANT or ASSOCIATE PROFESSOR with an interest in embryonic stem cells and formation of endoderm and endoderm-derived tissues. Prerequisite include an established record of independent investigation and peer-reviewed grant funding. Preference will be given to scientists (Ph.D. and/or M.D.) with research interests that complement and enhance ongoing research in islet and other cells of endodermal origin in the Departments of Surgery and Medicine.

Please send curriculum vitae, an outline of research plans, and the names of three references in electronic format (Word Document or PDF) to: **Dr. Michael Millis, Chief, Section of Transplantation Surgery, University of Chicago, Chicago IL, 5841 S. Maryland Ave., MC5027, Chicago IL 60637, e-mail: mmillis@surgery.bsd.uchicago.edu.**

THE UNIVERSITY OF CHICAGO

The University of Chicago is an Affirmative Action/Equal Opportunity Employer.

UNIVERSITY AT ALBANY
State University of New York

Assistant or Associate Professor
Faculty Positions - Life Sciences Research
College of Arts and Sciences

The College of Arts and Sciences, University at Albany invites applications for 3 tenure track positions at the Assistant or Associate Professor level. The University at Albany is engaged in a $100 million initiative in the Life Sciences that includes a new state-of-the-art research building and core facilities focused on Molecular Structure and Function. Successful candidates are expected to have or establish externally funded research programs working in the broad area of systems biology, including but not limited to the chemistry and molecular biology of development, genetic regulation, cell signaling or neuroscience utilizing any of a broad array of investigative technologies which may include structural, functional, high-throughput, and/or computational approaches.

The successful candidates will be able to interact with a broad group of research scientists http://www.albany.edu/lifesciences/ in the departments of Biological Sciences, Chemistry, Psychology, and Physics as well as in the greater Albany area. They will participate in the typical teaching responsibilities of the faculty and each appointment will be made in an academic department that is appropriate to their background and interests.

Qualification: Ph.D. and strong publication record. The Ph.D. must be from a college or university accredited by the U.S. Department of Education or an internationally recognized accrediting organization. Applicants must address in their applications their abilities to work with and instruct a culturally diverse population. Preferred candidates for assistant professor appointments should have completed productive post-doctoral training and show promise as independent, extramurally funded investigators. Preferred candidates for associate professor level appointments must have established records of significant scientific accomplishments and extramural research support. Finalists will be required to present a formal seminar on their research interests.

Send CV, statement of research interests, statement of teaching interests, and a minimum of 3 letters of reference by email to: **lifesciences@albany.edu**

Review of applications will begin November 15, 2006.

The University at Albany is an EEO/AA/IRCA/ADA employer.

BIOCHEMISTRY FACULTY POSITION

The Dept of Biochemistry at the Albert Einstein College of Medicine, Yeshiva University, is seeking a tenure-track Assistant Professor. Applicants should be developing novel or innovative approaches to fundamental questions of biological chemistry with links to human disease.

The College of Medicine is expanding with a new research building for genetic and translational medicine. This center will house over 30 new laboratories and is scheduled for completion in early 2008.

Research interests may complement those of existing faculty, including programs with broad application in Biochemistry, Chemical Biology and Structural Biology. Specific areas of interest include, but are not limited to, computational approaches to small molecule and macromolecular ligand binding, approaches to molecular evolution, and aspects of natural product discovery.

Candidates are expected to have a PhD or MD degree, postdoctoral experience and a strong record of accomplishment.

Applicants should send a curriculum vitae and a summary of research plans as a single PDF to: **BCsearch06@medusa.bioc.aecom.yu.edu.** Applications arriving before January 15, 2007 will receive full consideration. Letters from three or more references should be sent to the same email address. Other correspondence can be addressed to: **Search Committee, Dept of Biochemistry, Albert Einstein College of Medicine, Jack & Pearl Resnick Campus, 1300 Morris Park Ave, Bronx, NY 10461.** EOE.

ALBERT EINSTEIN COLLEGE OF MEDICINE
Advancing science, building careers

Population Geneticist

University of NEW ENGLAND

The University of New England invites applications for a tenure-track assistant professorship in the Department of Biological Sciences. Preference will be given to candidates with a strong quantitative background and research interests that complement existing departmental research. The successful individual is expected to develop an extramurally funded research program involving undergraduate and/or masters-level students and to teach courses in Biology, Biostatistics, Genetics and advanced courses in area of expertise.

Review of applications will begin December 2006.

*See **http://www.une.edu/hr** for details.*

UNE is an affirmative action and equal opportunity employer. We encourage people of all abilities, races, cultures, religions and genders to apply.

FACULTY POSITION IN BIOCHEMISTRY

Kansas City University of Medicine and Biosciences invites applications from outstanding individuals for appointment at the rank of Associate Professor or Professor in the Department of Biochemistry. We seek an individual with research interests in chronic diseases of aging (e.g. cancer, Alzheimer's disease); applicants who can further KCUMB's strategic areas of research focus in molecular biology, neurodegeneration, proteomics, and biophysics are especially encouraged to apply. The successful applicant will have a Ph.D. (or equivalent doctorate), a record of scholarly publications, a track record of progressive external grant funding, be willing to mentor graduate and medical students and be able to contribute effectively to an innovative instructional curriculum. For additional information contact Norbert Seidler, Ph.D., Chair, Department of Biochemistry, 1-800-234-4847, ext. 2207 or 816-283-2207, **nseidler@kcumb.edu**. Please visit **www.kcumb.edu** and click on 'Employment' to view remainder of ad and for CV submission directions.

EOE

KANSAS CITY UNIVERSITY OF MEDICINE & BIOSCIENCES

Assistant/Associate/Full Professor
University of California, Davis

Assistant/Associate/Full Professor, Comparative Medicine or Pathology, (tenure track). Assistant Professor preferred. This appointment is in the Department of Pathology, Microbiology and Immunology at the University of California at Davis. The successful candidate will be located at the University of California, San Diego, as an "In Residence" position and will participate in the UC Veterinary Medical Center-San Diego, a joint venture of UC Davis and UC San Diego. DVM (or equivalent) and PhD (or equivalent postdoctoral research training) required at appointment. ACVP board certification is preferred, if the candidate is a pathologist. Demonstrated aptitude/experience in teaching. Documented research record using contemporary/ molecular technologies for the characterization of disease pathogenesis or host defense. The research area is open but an emphasis in infectious diseases, cancer or neuropathology is preferred in order to build on areas of current strength. Potential and/or demonstrated ability in acquisition of extramural funding. Current extramural funding is preferred. Must possess excellent interpersonal and communication skills and a demonstrated ability to work with others in a collegial team atmosphere.

To receive fullest consideration, applications must be received by **November 30, 2006**; position opened until filled. Expanded position description at **http://www.vetmed.ucdavis.edu/pmi/PMIpage1.htm**. Submit letter of intent outlining special interest in the position, overall qualifications, experience, and career goals; CV; and names and addresses of three professional references to: **Dennis W. Wilson, Chairman, Department of Pathology, Microbiology and Immunology, School of Veterinary Medicine, University of California, Davis, Davis, CA 95616, Attn: Donna Roggenkamp.**

AA/EOE

The Jackson Laboratory

Scientific Curators

Professional positions are available as Scientific Curators with the Mouse Genome Informatics Program at The Jackson Laboratory. Successful candidates will be primarily responsible for data acquisition and analysis, evaluating and annotating data to be incorporated into the database, integrating information from disparate sources, and interacting with research laboratories and genome centers to facilitate data transfer. In addition, Curators take part in database and interface design by contributing biological perspectives to new data content and displays. Applicants should have a strong background in mammalian genetics, comparative genomics, or animal models of human disease. Experience in/knowledge of genetic engineering techniques, immunology, disease-specific areas, or embryonic development are preferred. Other desirable attributes include excellent writing/communication skills and the ability to work effectively in a team environment. Ph.D. degree in Life Sciences or M.S. with extensive experience required.

The Jackson Laboratory is one of the world's foremost centers for mammalian genetics research. Located in Bar Harbor, Maine, the lab is adjacent to Acadia National Park. Mountains, ocean, forests, lakes, and trails are all within walking distance. If you love high tech challenges but you're looking for a more natural environment, this could be the opportunity you've been searching for.

Interested applicants should apply online, checking off job requisition #SC-05. Please submit cover letter and resume as one document.

The Jackson Laboratory is an Equal Opportunity/Affirmative Action Employer.

www.jax.org

University of Hawai'i at Hilo
Academic Administrative Positions at the College of Pharmacy

The Hawaii State Legislature and the Board of Regents of the University of Hawaii has authorized the launch of a new College of Pharmacy (COP) at the University of Hawaii at Hilo located on the Big Island of Hawaii. Dean John M. Pezzuto and the University of Hawaii at Hilo invite applicants to join the academic administrative team and form a core faculty to initiate the mission of providing exemplary professional pharmacy education leading to the degree of Pharm. D. A goal of the College is to advance excellence in pharmacy practice while capitalizing on translational research programs designed to enhance pharmaceutical healthcare throughout the world. Advantage will be taken of the unique and creative energies of Hawaiian, Pacific Islanders and other diverse cultures in the nexus of cultural beliefs and practices with innovations and discoveries for global health and well being.

Associate Dean for Academic Programs: Position No: 89468. The successful applicant will provide leadership in development and ongoing evaluation of the curriculum for the Pharm. D. program. This Associate Dean will oversee priorities for the College in academic affairs. These include, but are not limited to, securing ACPE accreditation; recruitment, admission and graduation of professional students; hiring and retention of faculty; management of staff support personnel and resources; other relevant activities to the academic offerings of the College. The candidate will be a member of the Dean's administrative council. Minimum qualifications are: doctoral degree (PhD or professional doctorate such as PharmD, MD, JD); three (3) years relevant experience; eligibility for an academic/clinical appointment at the University of Hawaii at Hilo.

Associate Dean for Research: Position No: 89469. The successful applicant will provide leadership in the scholarship of pharmaceutical and interdisciplinary sciences, and promote interactions in the University of Hawaii system and globally among other academic institutions and/or pharmaceutical industries. This Associate Dean will oversee the research mission and direct the establishment and continuation of funded research programs among the faculty. The candidate will be a member of the Dean's administrative council. Minimum qualifications are: doctoral degree (PhD or professional doctorate such as PharmD, MD, JD); three (3) years relevant experience; eligibility for an academic appointment at the University of Hawaii at Hilo.

The University of Hawaii at Hilo is one of two, 4-year institutions in the University of Hawaii system (see **http://www.uhh.Hawaii.edu**). Information about the pharmacy program can be accessed at **http://www.uhh.hawaii.edu/academics/pharmacy**. Review of applications will begin November 15, 2006, and continue until the positions are filled. Candidates should submit a cover letter summarizing his/her interests and qualifications for the position, a current C.V. and the names of three (3) professional references including postal, email address and telephone contact information. For a job description, specific position requirements and desirable qualifications please go to **www.uhh.hawaii.edu/uhh/hr/jobs.php**. Applications should be submitted to:

Dr. Daniel Brown, Chairperson
c/o Yolanda Belog
Search Committee for (position you are applying for)
University of Hawaii at Hilo
200 W. Kawili St.
Hilo HI 96720

The University of Hawaii at Hilo is an Equal Employment Opportunity/Affirmative Action Employer D/M/V/W.

POSTDOC OPPORTUNITIES

POSTDOCTORAL POSITIONS, MOLECULAR MICROBIOLOGY AND PATHOGENESIS OF BACTERIAL AND VIRAL INFECTIONS. NIH training grant-funded Postdoctoral Positions are available at the University of Colorado Health Sciences Center to study molecular mechanisms of bacterial infections (with **Randall Holmes, Michael Schurr, Michael Vasil, Andres Vazquez-Torres,** or **Martin Voskuil),** molecular aspects of viral infections (with **David Barton, Thomas Campbell, Robert Garcea, Donald Gilden, Kathryn Holmes, Jerome Schaack, Kenneth Tyler,** or **Linda Van Dyk),** molecular basis of innate immunity (with **Charles Dinarello, Sonia Flores,** or **Andres Vazquez-Torres)** or structural biology of microbial pathogenesis (with **Mair Churchill).** See **website: http://www.uchsc.edu/sm/microbio/** for information about many of our research programs. Research facilities, grant funding, and training environment are excellent. *Applicants for these positions must be citizens or permanent residents of the United States.* Candidates with Ph.D. or equivalent research degrees must have experience in microbiology, bacteriology, virology, immunology, molecular biology, genetics, biochemistry, cell biology, structural biology or a related field. Candidates with M.D., D.V.M., or equivalent clinical degrees must have demonstrated competency for research related to our Program. Individuals from underrepresented groups are encouraged to apply. Compensation is determined by NIH policies. Submit curriculum vitae, bibliography, and names of three professional references to: **Training Program Director, University of Colorado Health Sciences Center at Fitzsimons, Microbiology Department, Mail Stop 8333, P.O. Box 6511, Aurora, CO 80045.** *The University of Colorado Health Sciences Center is committed to Equal Opportunity and Affirmative Action.*

POSTDOCTORAL FELLOWSHIP IN NEURO-ONCOLOGY
University of Virginia

A full-time Postdoctoral Position is available in a laboratory dedicated to finding new therapies for brain tumors. The project will focus on the biology of the Notch pathway and its downstream mediators in brain tumors, including developing them as therapeutic targets.

Experience in cell culture, mouse studies, RT-PCR, and immunoblotting advantageous. Candidates must have a Ph.D. degree and have prior experience in either cancer research or neurobiology. The position is open beginning in November 2006. To apply, please send curriculum vitae and names/e-mail addresses of three references via e-mail to: **Dr. Benjamin Purow, University of Virginia School of Medicine, e-mail: purowb@mail.nih.gov** (through October 31, 2006) or **e-mail: bpurow@gmail.com.**

TWO POSTDOCTORAL POSITIONS to study the role of chromatin structure and gene expression in DNA repair in yeast, cell extracts and mammalian cells (e.g., **Svedružić et al.,** *J. Biol. Chem.* **280:**40051, 2005; **Gong et al.,** *Nature Structural and Molecular Biology,* published online October 1, 2006). Training in biochemistry, physical biochemistry or molecular biology/genetics is preferred. **Dr. Michael J. Smerdon, Regents Professor, Washington State University, School of Molecular Biosciences, Pullman, WA 99164-4660 (website: http://www.wsu.edu/~smerdon/index.html).** Send statement of interests, resume, and names of three references to **e-mail: dsmerdon@wsu.edu.** *Washington State University is an Equal Opportunity Educator and Employer. Members of protected groups are encouraged to apply.*

POSTDOCTORAL FELLOWSHIP to study macrophage migration inhibitory factor in bladder/prostate inflammation and cancer. Candidate should have experience with cell culture, transfection, protein isolation and purification, western blotting, enzyme-linked immunosorbent assay, qRT-PCR, gene array, cystometrograms. Salary in accordance to NIH recommendations and commensurate with experience. Benefits available. *Only U.S. citizens, less than two years of postgraduate should apply.*

POSITIONS OPEN

Research Corporation is seeking a talented scientist with expertise at the interface of the physical and biological sciences to assist the foundation in its support of scientists and the advancement of science. The position title is **PROGRAM OFFICER,** and responsibilities include the processing and evaluation of research proposals, evaluation of one-of-a-kind opportunities in science and science education, visiting colleges and universities on behalf of the foundation, representing the foundation at professional meetings, and assessing trends and opportunities in the physical and life sciences. Applicants must have a Ph.D. degree, which positions one to work facilely at the interface of chemistry, physics and biological science; excellent communication skills; the ability to work well with others, including a wide range of scientists and administrators at primarily undergraduate institutions and research universities; and an interest in working across the disciplines in the physical and life sciences. Applicants must have five or more years of experience in a permanent position as a faculty member or an industrial/government scientist and a demonstrated record of accomplishment within this setting. In particular, a successful record of grantsmanship and independent publication is expected. Salary is commensurate with experience and qualifications and includes an outstanding package of benefits.

This is a remarkable opportunity to work in a cohesive, well-supported office as part of a small team of highly dedicated scientists interested in the advancement of scientists and programs of science. Program Officers work with a great deal of independence, have significant opportunities for professional development, and travel regularly to colleges and universities to meet with faculty and administrators. The Foundation's science advancement programs are focused on helping faculty, usually early in their careers, to establish sustainable programs of research and education. The Foundation's offices are located in Tucson, a vibrant southwestern community of more than one-half million residents, surrounded by mountains and the Sonoran Desert, served by an international airport, with a world-class university, significant programs in the creative and performing arts, and with nearly unlimited opportunities for outdoor activities.

Information about the foundation and its programs can be found on **website: http://www.rescorp.org.** Application should include vitae, the names and addresses of three individuals who could serve as references, and a one to two-page statement that addresses why the applicant would undertake a career in science advancement. Applications will be reviewed as received. Send completed application to: **Dr. Raymond Kellman, Vice President; Research Corporation; 4703 East Camp Lowell, Suite 201; Tucson, AZ 85712.**

POSTDOC OPPORTUNITIES

The training program in cancer biology at Wake Forest University Health Sciences has an immediate opening for a two-year **POSTDOCTORAL TRAINING POSITION** supported by an Institutional Training Grant from the National Cancer Institute. The trainee will conduct research mentored by training faculty in one of a wide range of possible disciplines, including carcinogenesis, DNA damage and repair, gene-environment interactions, cell biology of cancer, signal transduction, apoptosis, radiation biology, and novel therapeutics. Applicants should consult the **website: http://www1.wfubmc.edu/canbio/** for additional information. Applicants must hold a Ph.D., M.D., or D.V.M., and *must be citizens or permanent residents of the United States.* Preference will be given to applicants within three years of obtaining their doctoral degree. Interested individuals should send curriculum vitae and three letters of reference to: **Dr. Steven Akman, Director of Cancer Biology Training Program, Wake Forest University Health Sciences, Medical Center Boulevard, Winston-Salem, NC 27157.** *Equal Opportunity/Affirmative Action Employer. Minority applicants are encouraged.*

POSITIONS OPEN

The Biology Department of Manhattan College (New York) seeks to fill three tenure-track positions at the **ASSISTANT/ASSOCIATE PROFESSOR** level for fall 2007 in genetics, microbiology, and vertebrate biology.

Successful candidates will teach basic undergraduate courses for majors in their areas of expertise as well as several other courses for majors and nonmajors. Initiating and maintaining a research program with undergraduate involvement is expected, as is publication in the peer-reviewed literature. Upper-level undergraduate course assignments will include developmental biology, histology, immunology, molecular biology, neurobiology, cell biology, and systemic physiology. Please indicate which of these upper-level courses you are capable of teaching. Also provide a list of space, equipment, and support needs for your research program.

Please send your curriculum vitae, documentation of completed Ph.D. and a list of three references to:

Biology Search Committee Chair
c/o Geraldine Muranelli
(E-mail: geraldine.muranelli@manhattan.edu)
School of Science, Hayden Hall
Manhattan College
Riverdale, NY 10471

Electronic submission of materials is encouraged. Review of applications will begin on 27 November 2006. Manhattan College is an independent Catholic co-educational Institution in the Lasallian tradition located in the Riverdale section of New York City. We expect our faculty, administration, and staff to be knowledgeable about our mission and to make a positive contribution to that mission. Women and minorities are encouraged to apply. We are committed to a diverse campus community.

Affirmative Action/Equal Opportunity Employer Minorities/Females/Persons with Disabilities/Veterans.

FORENSIC SCIENTIST. Ph.D. required, rank, area of research specialization, and tenure home open. The successful candidate will be a Forensic Scientist with training that will enhance the interdisciplinary Forensic Science Program. A viable program of externally funded research related to theoretical or applied forensic science is expected. Teaching experience, a molecular biology perspective, or analytical chemistry perspective in forensic science or clinical experience in a forensic laboratory are highly desirable. Teaching responsibilities may include an introductory course in forensic science, a forensic evidence analysis course, and other existing or new courses that complement the program and enhance its quality and competitiveness for future accreditation. Send curriculum vitae, statement of teaching and research plans, and contact information for three references to: **Forensic Search, College of Arts and Sciences, 290 Centennial Drive, Stop 8038, University of North Dakota, Grand Forks, ND 58201.** Screening begins in early November 2006, and continues until position is filled. *The University of North Dakota is an Equal Opportunity Employer. Women and minorities are encouraged to apply.*

CURATOR OF DIATOMS. Must establish and maintain an internationally recognized program of externally funded research in systematics, taxonomy, evolution, ecology or related disciplines. Career-track position. Includes curatorial oversight of the Academy's Diatom Herbarium and providing taxonomic support the Phycology Section in the Academy's Patrick Center.

A Ph.D. and demonstrated expertise in diatom systematics are essential. Postdoctoral experience, familiarity with diatom collections, and use of diatoms as environmental indicators, are desirable. Position available January 1, 2007; review begins November 15, 2006. For more, see **website: http://www.ansp.org/about/employment.php#937.** Send or e-mail curriculum vitae, statement of research interests, representative publications, and names, addresses, telephone numbers, and e-mail addresses of four references to: **Maria Eife, Office Manager #937,The Academy of Natural Sciences, 1900 Benjamin Franklin Parkway, Philadelphia, PA 19103-1195,** or **e-mail: eife@ansp.org.**

UNIVERSITY AT ALBANY
State University of New York

ASSISTANT PROFESSORS

FACULTY POSITIONS IN BIOLOGICAL SCIENCES

The Department of Biological Sciences, University at Albany, State University of New York, invites applications for 2 tenure-track positions at the level of Assistant Professor.

(1) Ecology or Evolution of Infectious Disease: The Department is the focal point for a regional multidisciplinary emphasis on the ecology and evolution of infectious disease providing opportunities for broad collaborations.

(2) Forensic Molecular Population Biology: The Department provides graduate training in Forensic Molecular Biology and the successful candidate will be expected to participate in that program and to train doctoral students in evolutionary or molecular biology.

Preferred applicants will have postdoctoral experience, an outstanding record of achievement in research and the potential to establish an externally funded research program. All faculty participate in both undergraduate and graduate teaching and in graduate training in research.

For details concerning each position, see

http://www.albany.edu/biology/announcements

Applicants must submit by email a curriculum vitae, a summary of research and teaching interests, and should arrange submission of three or more letters of reference. The Ph.D. degree must be from a college or university accredited by the U.S. Department of Education or an internationally recognized accrediting organization. Applicants must address in their applications their abilities to work with and instruct a culturally diverse population.

For the position in Ecology or Evolution of Infectious Disease, send materials to ecology@albany.edu. For the position in Forensic Molecular Population Biology, send materials to forensic@albany.edu. Review of applications begins Nov. 15, 2006, but applications will be accepted until the positions are filled. Positions are contingent on final budget approval.

SALARY: Competitive salary & setup package

STARTING DATE: Fall 2007

The University at Albany is an EEO/AA/IRCA/ADA employer.

Assistant/Associate Professor, Anatomy
School of Medicine
Southern Illinois University Carbondale

The Department of Anatomy at Southern Illinois University School of Medicine-Carbondale invites applications for a tenure-track faculty position at the Assistant or Associate Professor level. Qualified candidates must have a Ph.D., M.D., or equivalent degree, and at least two years of postdoctoral experience with demonstrated ability to perform vigorous independent research. Opportunity for research collaboration exists within several basic science and clinical departments with strengths in neuroscience, cancer, and cell and molecular biology among other areas. Preferential consideration will be given to those with teaching experience or training in the anatomical sciences (histology/cell biology, gross anatomy, embryology, or neuroanatomy).

Applicants at the Associate Professor level should have similar rank in their present positions, an extramurally funded research program and substantial research productivity. This is a 12-month, state-funded position with a competitive salary, substantial startup package and spacious lab facilities. The community surrounding Carbondale is home to a rich variety of peoples including over 20 thousand university students and is located two hours southeast from St. Louis on the border of the Shawnee National Forest. Faculty and students enjoy the best of several worlds: big city availability, scenic getaways, outdoor recreation, a vibrant university and a growing research culture.

This is a security-sensitive position. Before any offer of employment is made, the University will conduct a pre-employment background investigation, which includes a criminal background check. Review of applications will begin **January 15, 2007** and will continue until the position is filled. Applicants are asked to provide a curriculum vitae, descriptions of teaching interests and research plans, and must arrange to have three letters of reference sent to: **Search Committee, Department of Anatomy, School of Medicine, Southern Illinois University Carbondale, Mail code 6523, 1135 Lincoln Drive, Carbondale, IL 62901.**

SIUC is an Affirmative Action/Equal Opportunity Employer that strives to enhance its ability to develop a diverse faculty and staff and to increase its potential to serve a diverse student population. All applicants are welcomed and encouraged and will receive equal consideration.

CHAIR
University of California, Davis
Department of Pharmacology

CHAIR, Department of Pharmacology. The University of California, Davis School of Medicine is seeking candidates for the Chair of the Department of Pharmacology. The UC Davis Department of Pharmacology is in the midst of rapid and vigorous growth, as part of a major expansion of the basic biomedical sciences in the School of Medicine. Research in the Department of Pharmacology includes a broad range of experimental approaches, bringing together an outstanding group of faculty with expertise in the biochemical, molecular, and cellular aspects of modern Pharmacology. The research in the department can be organized into two highly interrelated focus areas that include: (1) characterizing the mechanisms by which information is transferred from the extracellular environment to the nucleus or between cells within the organism; and (2) developing methods and reagents that will interfere with or enhance the information transfer. We seek an outstanding scientist with a superb record in research, who complements and will extend our existing departmental focus areas and be consistent with the School of Medicine's strategic plan. A copy of the strategic plan can be found at the following web address: **http://www.ucdmc.ucdavis.edu/dean/** We seek an individual who will provide visionary and dynamic academic leadership to a vibrant and young department.

The Chair will lead a department that currently has 10 full-time faculty, nine of whom have joined the department within the last two years. The Pharmacology department is housed in the newly opened Genome and Biomedical Science Facility on the Davis campus, and has strong links to the new UC Davis Genome Center and the Center for Neuroscience. Additional information about the department is available at: **http://www.ucdmc.ucdavis.edu/pharmacology**/. The Chair will also be responsible for continued growth of the Department, with the addition of 3 new state-funded tenure track faculty positions. Each new position will be accompanied by the resources needed to ensure recruitment of outstanding faculty.

The successful candidate will be an internationally recognized scientist with an active research program who has a demonstrated record of leadership, in research, education, mentoring, and administration and who qualifies for appointment at the Full Professor level. The candidate should have a broad, strong vision for basic and translational science, and be prepared to lead the department in the School of Medicine's multi-departmental quest for excellence. The candidate should have demonstrated ability to meet the challenges of academic medicine and to work cooperatively and collegially within a diverse environment. The candidate must possess a Ph.D., M.D., M.D./Ph.D. or equivalent. This is a state funded position (FTE) within the School of Medicine.

Please forward: (1) curriculum vitae; (2) statement of research and administrative background; and (3) names and addresses of five references to: **Pharmacology Chair Search Committee,** via email to **Janice.weir@ucdmc.ucdavis.edu**, or via regular mail to: **Janice Weir, c/o Office of Academic Affairs, School of Medicine, University of California, Davis, Medical Center, PSSB Suite 2500, 4150 V Street, Sacramento, CA 95817**.

For Full consideration, applications must be received by **December 31, 2006**. The position will remain open until filled.

The University of California is an Affirmative Action/ Equal Opportunity Employer.

POSITIONS OPEN

ROSALIND FRANKLIN UNIVERSITY OF MEDICINE AND SCIENCE

ASSISTANT/ASSOCIATE PROFESSOR
Mebrane Protein Structural Biology

As part of a University-wide initiative, the Department of Biochemistry and Molecular Biology (BMB) continues to undergo significant expansion and invites applications for a tenure-track Assistant or Associate Professor in the area of membrane protein structural biology. We seek candidates employing cutting-edge biophysical techniques that will provide fundamental insight into the structure-based mechanisms of membrane proteins. Although preference will be given to candidates using X-ray crystallography or cryo-electron crystallography, outstanding candidates employing other biophysical approaches are also encouraged to apply. BMB is a well-funded active Department that enjoys strong University commitment to development of membrane protein structural biology. In addition to faculty recruitment in this area, the University commitment includes recent development of the Rosalind Franklin Structural Biology Laboratories (consisting of state-of-the-art facilities for X-ray diffraction, mass spectrometry/proteomics, and electron paramagnetic resonance) and a biophysical instrumentation facility, as well as access to the nearby A. P. S. via participation in the Southeast Regional Collaborative Access Team beamline consortium. Candidates at the Assistant Professor level must have outstanding research potential and a commitment to excellence in teaching, whereas applicants at the Associate Professor level must demonstrate outstanding research accomplishment including national recognition and extramural funding, as well as a track record in graduate training. The successful candidate will receive a highly competitive salary, an attractive startup package and space, and is expected to develop or maintain an externally funded research program, as well as teach at the medical and graduate school levels. Further information about the Department can be viewed at **website: http://www.rosalindfranklin.edu/cms/biochem.** Interested applicants should submit their curriculum vitae, a two-page summary of research interests, copies of representative publications, and the names of at least three references to: **Dr. Ronald S. Kaplan, Chair, Department of Biochemistry and Molecular Biology, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Road, North Chicago, IL 60064,** or as an attached document to **e-mail: ronald.kaplan@rosalindfranklin.edu.** Review of applications will begin immediately and will continue until the position is filled. *Rosalind Franklin University of Medicine and Science is an Equal Opportunity/Affirmative Action Employer.*

SENIOR SCIENTIST

A Senior Scientist position is immediately available at BioProtection Systems Corporation in Ames, Iowa. We are interested in candidates with expertise in immunology/innate immunity and the relevance to infectious diseases. Substantial background, experience, and training in cellular immunology is required, with particular emphasis on the establishment of viral immunity. The successful candidate will supervise the immunological analysis of our vaccine development program. Applicants must have a Ph.D. in immunology or virology (or a related field). Experience with in vivo mouse models of infectious disease is beneficial. Postdoctoral research experience is required for this position. Salary will be based on qualifications.

Please send or e-mail your confidential curriculum vitae to the attention of:

Joseph E. Nash, Human Resources
BioProtection Systems Corporation
2901 South Loop Drive, Suite 3360
Ames, IA 50010-8646

POSITIONS OPEN

ASSISTANT PROFESSOR, MAMMALIAN DEVELOPMENTAL GENETICS. The Biochemistry and Cellular and Molecular Biology (BCMB) Department at the University of Tennessee seeks to fill a tenure-track faculty position at the Assistant Professor level to begin in August 2007. We will particularly welcome applications from individuals who apply genomic or proteomic methods and/or use mouse genetic models to address problems in developmental biology, and from individuals with interests in developmental neurobiology, but outstanding applications from individuals in all areas of developmental genetics will be considered. The successful candidate for this position will benefit from interactions with strong research groups within the BCMB Department and in other units on campus and at the nearby Oak Ridge National Laboratory in neurobiology, chromatin and chromosome dynamics, biology of cancer and aging, cell division and cell cycle, structural biology, enzyme mechanisms, mouse genetics/genomics, proteomics and computational biology. The successful applicant will be expected to develop an independent, externally funded research program in mammalian developmental genetics, to provide state-of-the-art training for graduate students and postdoctoral researchers, and to contribute to the teaching mission of the BCMB Department at both the undergraduate and graduate levels. Required qualifications include a Ph.D. and postdoctoral experience in relevant areas of biology, evidence of significant scientific productivity, and a commitment to an integrated program of teaching and research. The University welcomes and honors people of all races, creeds, cultures, and sexual orientations, and values intellectual curiosity, pursuit of knowledge, and academic freedom and integrity.

Interested candidates should send a cover letter, a resume, a description of research experience and of the proposed research program, and the names of three individuals who can provide letters of reference to: **Bruce McKee, Head, Biochemistry and Cellular and Molecular Biology Department, M407 WLS, University of Tennessee, Knoxville, TN 37996-0840.** Review of applications will begin on November 1, 2006, and continue until the position is filled.

The University of Tennessee is an Equal Employment Opportunity/Affirmative Action/Title VI/Title IX/Section 504/ADA/ADEA Institution in the provision of its education and employment programs and services.

TENURE-TRACK ASSISTANT PROFESSOR POSITION
The Department of Structural and Cellular Biology and Tulane Cancer Center

The Department of Structural and Cellular Biology, Tulane University School of Medicine, and the Louisiana Cancer Research Consortium (LCRC) are seeking applications for a tenure-track faculty position at the Assistant Professor level. The LCRC is a partnership between the Tulane Cancer Center and the Louisiana State University Stanley Scott Cancer Center to establish an NCI-designated Cancer Center in New Orleans. Candidates with an emphasis in signaling and cancer particularly the areas of metastasis and angiogenesis of breast, prostate, or ovarian cancer will be considered. The Department of Structural and Cellular Biology and the Tulane Cancer Center are both undergoing major expansion and outstanding startup, facilities, and environment will be provided. Candidates must have an earned doctorate and at least two years of productive postdoctoral research experience. Candidates with movable extramural research support (NCI) are preferred but highly qualified candidates recently out of postdoctoral positions will be considered. Please submit applications including curriculum vitae, summary of research interests, summary of research and teaching interests, and three letters of recommendation to: **Dr. Steven M. Hill, Department of Structural and Cellular Biology, SL49, Tulane University Health Sciences Center, School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112.** Applications will be accepted until the position is filled. *Tulane University is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.*

POSITIONS OPEN

UT UNIVERSITY MEDICAL CENTER
THE UNIVERSITY OF TOLEDO

TWO TENURE-TRACK FACULTY POSITIONS
Immunology

The Department of Medical Microbiology and Immunology at the University of Toledo College of Medicine, formerly known as Medical University of Ohio **(website: http: www.meduohio.edu),** is seeking to hire two tenure-track faculty members at the level of **ASSISTANT/ASSOCIATE PROFESSOR.** Immunology has recently been identified as a specific target area of institutional programmatic growth. Candidates must hold a Ph.D., M.D., or equivalent degrees and have at least three years of relevant postdoctoral experience (Assistant Professor) or faculty appointment (Associate Professor). A successful candidate will be expected to develop/maintain an externally funded, basic and/or translational research program in the fields, including (but not limited to) transplant immunology, autoimmunity, immune responses to infectious agents, and vaccine development and to participate actively in the departmental teaching mission. Applications should include: (a) curriculum vitae, (b) a brief summary of research interests, past accomplishments, and future plans, and (c) names and addresses of three references. All materials should be sent to: **Akira Takashima, M.D., Ph.D., Professor and Chairman, Department of Medical Microbiology and Immunology, University of Toledo, Health Science Campus, 3000 Arlington Avenue, Toledo, OH 43614-2598.** Applications will be reviewed immediately upon receipt. *The University of Toledo is committed to diversity and equal opportunity. Applications from women and minority candidates are strongly encouraged.*

YALE UNIVERSITY SCHOOL OF MEDICINE
Department of Genetics

The Department of Genetics at the Yale University School of Medicine is seeking to recruit one or more outstanding candidates to become **ASSISTANT PROFESSOR OF GENETICS.** Successful applicants will be provided generous startup funds and space and will establish strong independent research programs; areas of particular interest include genetics and genomics of vertebrate model organisms, cancer and other human diseases, and computational genomics. We strongly encourage applications from women and minority candidates. Curriculum vitae, a concise statement of research plans, and three letters of recommendation should be sent electronically and with hard copy to:

Richard P. Lifton, M.D., Ph.D.
Chairman
Department of Genetics
Yale University School of Medicine
P.O. Box 208005
New Haven, CT 06520-8005
E-mail: genadm@e-mail.med.yale.edu

An Equal Opportunity/Affirmative Action Employer.

RESEARCH ASSOCIATE (ASSISTANT PROFESSOR) POSITION available in the Department of Neurology for the study of the pathogenesis of amyotrophic lateral sclerosis. Candidates must have a doctorate in biological sciences or a related field with at least four years of experience in experimental neuroscience. Salary will be commensurate with background and experience. Send curriculum vitae, a personal research statement, provide three letters of reference, and the best publications to **Dr. Raymond P. Roos** as hard copy: **Department of Neurology, MC2030, University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637 (fax: 773-834-9089)** or **via e-mail: rroos@neurology.bsd.uchicago.edu** with e-files. Screening of applications will continue until position is filled. *The University of Chicago is an Affirmative Action/Equal Opportunity Employer.*

ST. MARY'S UNIVERSITY

Fostering
Academic Excellence And
Spiritual Growth

ASSISTANT PROFESSOR-DEVELOPMENTAL BIOLOGIST

St. Mary's University of San Antonio, a private, Catholic university invites applications for a full-time tenure track faculty position in the Department of Biological Sciences beginning August 2007.

The primary responsibilities of this position will be teaching two courses with associated laboratory per semester. These courses will include embryology/developmental biology and introductory biology as well as a course to be developed by the candidate in his/her area of specialty. While teaching is the primary function of the position, research, especially involving undergraduates, is expected of the successful candidate. The presence of an active biomedical research community in the San Antonio area provides the opportunity to establish collaborative research projects in many fields. A Ph.D. in Biology or a related discipline is required and postdoctoral experience is preferred.

Founded in 1852 and operated by the Society of Mary, St. Mary's University is a Hispanic Serving Institution with a proven history of preparing undergraduate science students for careers in health professions and research. For more information visit the university web site at **www.stmarytx.edu** or contact the chair at: **cnolan@stmarytx.edu** or **210-436-3241**.
Salary is commensurate with experience and is accompanied by a strong benefits package. All qualified applicants are welcome; minorities and women are encouraged to apply.

Applicants should submit a letter of application detailing interest in the position and a description of teaching and professional development goals, a curriculum vita, copies of graduate transcripts, the e-mail addresses and telephone numbers of references, and have three letters of recommendation sent to:

Dr. Colleen J. Nolan, Chair
Department of Biological Sciences
St. Mary's University
San Antonio, TX 78228-8607

Electronic submission of applications is encouraged, however, incomplete applications may not be considered. Review of applications will begin November 25, 2006 and will continue until a suitable candidate is identified. St. Mary's University is an Equal Opportunity Employer.

Tulane University

Two Tenure Track Positions
Department of Biomedical Engineering

The Department of Biomedical Engineering at Tulane University is pleased to invite applications for two tenure track faculty positions that will be available as early as January 2007. The Department of Biomedical Engineering was founded in 1977, has a full strength program of 13 full-time faculty positions, and an ABET accredited undergraduate program with approximately 200 undergraduate majors and 50 graduate students. Since July 2006, the Biomedical Engineering has been administratively located in the Division of Biological Sciences and Engineering in the new School of Science and Engineering. This new academic structure is enormously beneficial to the Department of Biomedical Engineering because of the strong emphasis on interdisciplinary interactions, with an administrative structure that reduces the overhead associated with these interactions.

We are committed to a major increase of an existing strength in the area of **biotransport** phenomena. Preferred candidates will use either **imaging** approaches for experimental investigation, and/or theoretical and **computational** approaches for modeling and simulation. We are specifically interested in candidates who link biotransport investigations of the neurological system, the pulmonary system or the eye to clinically important pathologies.

Excellent collaborative research opportunities exist in the School and with various centers and institutes at Tulane including the Health Sciences Center, the Center for Computational Sciences and the interdisciplinary program in Neurosciences. Louisiana has recently developed LONI (Louisiana Optical Network Infrastructure), which connects the State's major research institutions with high-speed bandwidth (40 Gigabits/s) connecting an approximately 100TFlop/s distributed grid-based computing facility that presently exceeds the capacity of most national facilities.

Applicants must have an earned doctorate, and will be expected to teach undergraduate and graduate courses and to develop an externally funded research program, consistent with having a fundamental interest in both teaching and research. These positions are subject to a final university determination on funding. Rank and salary are dependent upon candidate qualifications. Senior candidates will be considered for the recently established **John and Elsie Martinez Biomedical Engineering Chair**.

Please send a CV, a brief description of research and teaching interests, and names and addresses of three references to: **Faculty Search Committee, Department of Biomedical Engineering, Boggs Center, Suite 500, Tulane University, New Orleans, LA 70118-5674**. PDF applications may be submitted to **bmen-info@tulane.edu**. More information about the Department of Biomedical Engineering can be found at: **http://www.bmen.tulane.edu**.

Tulane University is an Affirmative Action - Equal Opportunity Employer.

Senior Research Biologist - Neuroscience

Merck & Co. Inc., established in 1891, is a global research-driven pharmaceutical company dedicated to putting patients first.

Join us and experience our culture first-hand – one of strong ethics and integrity, diversified experiences and a resounding passion for improving human health. As part of our global team, you will have the opportunity to collaborate with talented and dedicated colleagues while developing and expanding your career.

We currently have an opening for a **Senior Research Biologist** - **Neuroscience** in our Molecular Profiling Department. This position will play a leading role in the design and analysis of large scale gene expression profiling programs for biomarker and novel target discovery programs in support of our Neuroscience therapeutic area research franchises, including Alzheimer's Disease, Stroke, Pain, Sleep and Psychiatric Diseases. Specifically, the successful candidate will collaborate with biologists and chemists in the neuroscience franchise to utilize Molecular Profiling techniques including gene expression, genotyping, proteomics, metabolomics, and genome-wide siRNA screening to support drug discovery and development programs in the Neurosciences. In addition, this position will work with licensing professionals to review external opportunities, and will be expected to publish patents and peer-reviewed scientific papers.

Qualifications include: Ph.D. and/or M.D. plus three to six years of post-doctoral experience required, with extensive experience and knowledge of neuroscience in general and neurodegenerative disease in particular. Preference will be given to candidates with extensive training in the interpretation of large gene expression profiling data sets, strong statistical skills, and relevant experience in the development of clinically validated biomarkers. Excellent communication and organizational skills are essential.

Consistently cited as a great place to work, we discover, develop, manufacture and market a wide range of vaccines and medicines to address unmet medical needs. Each of our employees is joined by an extraordinary sense of purpose – bringing Merck's finest achievements to people around the world.

We offer an excellent salary and an industry-ranked benefits program, including tuition reimbursement, work-life balance initiatives and developmental programs at all levels. Merck's retirement package includes a pension plan and one of the best 401(k) plans in the nation.

To be considered for this position, please visit our career site at **www.merck.com/careers** to create a profile and submit your resume for Job Number SCI003020.

Merck is an equal opportunity employer, M/F/D/V – proudly embracing diversity in all of its manifestations.

MERCK

Our work is someone's hope. Join us.
Where patients come first – Merck.

POSITIONS OPEN

DIRECTOR, DIVISION OF HUMAN RESOURCE DEVELOPMENT
National Science Foundation, Arlington, Virginia

NSF's Directorate for Education and Human Resources seeks candidates for the position of Director, Division of Human Resource Development (HRD). The Division serves as a focal point for NSF's agency-wide commitment to enhancing the quality and excellence of science, technology, engineering, and mathematics (STEM) education and research through broadening participation by underrepresented groups and institution. Information about the Division's activities may be found at **website: http://www.nsf.gov/ehr/hrd/about.jsp.**

Appointment to this Senior Executive Service position may be on a career basis, on a one to three-year limited term basis, or by assignment under the Intergovernmental Personnel Act (IPA) provisions.

Announcement S20070006, with position requirements and application procedures are posted on NSF's home page at **website: http://www.nsf.gov/about/career_opps/.**

Applicants may also obtain the announcements by contacting **Executive Personnel Staff** at **telephone: 703-292-8755** *(hearing-impaired individuals may call TDD 703-292-8044).* Applications must be received by November 29, 2006.

NSF is an Equal Opportunity Employer.

FACULTY POSITION IN CHEMICAL ENGINEERING
Princeton University

The Department of Chemical Engineering seeks outstanding applicants for a tenure-track position at the **ASSISTANT PROFESSOR** level, effective as early as July 1, 2007. The successful candidate should have a Ph.D. in chemical engineering or related field, demonstrated excellence in academic research, and a strong commitment to teaching and advising undergraduate and graduate students. Applicants should send curriculum vitae, a detailed description of teaching and research interests, reprints of selected publications, and the names and addresses of at least three references to: **Faculty Search Committee, Department of Chemical Engineering, Princeton University, Princeton, NJ 08544-5263.** Applicants are encouraged to apply before December 1, 2006. For information about applying to Princeton and how to self-identify, please link to **website: http://web.princeton.edu/sites/dof/ApplicantsInfo.htm.** *Princeton University is an Equal Opportunity/Affirmative Action Employer. Women and minority candidates are encouraged to apply.*

EPIGENETICS/GENOME STABILITY

The Department of Biochemistry and Biophysics and the Wilmot Cancer Center at the University of Rochester Medical Center invite applications for a tenure-track position in epigenetics/genome stability at the **ASSISTANT PROFESSOR** level or higher. Applicants employing genetic methods in mammalian systems, especially those in areas complementing existing strengths in chromatin function and repair, signaling, and cancer cell biology are invited. Submit a curriculum vitae, statement of research accomplishments and plans and letters of recommendation to: **Robert Bambara, P.O. Box 712, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642.** See **websites: http://dbb.urmc.rochester.edu** and **www.stronghealth.com/services/cancer** for details. *The University of Rochester is an Equal Opportunity/Affirmative Action Employer.*

SCIENTIST/FACULTY (ALL LEVELS)
Pennsylvania Institute for Hepatitis and Virus Research of the Hepatitis B Foundation of America Scientist/Faculty

The Institute for Hepatitis and Viral Research (IHVR) is a nonprofit dedicated to mission-oriented research and takes a team approach that is funded in part by NIH and state grants. Stimulating environment with faculty appointments through Drexel University College of Medicine possible. Ph.D. or equivalent. Appointments at Postdoctoral or all levels beyond possible. Beautiful setting near Philadelphia/Princeton.

MOLECULAR VIROLOGIST: West Nile Virus antiviral program. Lead discovery of antivirals or mechanism of action project.

GLYCOBIOLOGIST: Cancer detection, protein folding studies, proteomics. Mass spectrometry/high performance liquid chromatography.

IMMUNOLOGIST/ASSAY DEVELOPMENT: Help implement a new cancer and fibrosis detection assay.

BIOTECHNOLOGY COORDINATOR: Helps in our nurture of nascent biotechnology companies. Business and science background ideal.

Please indicate position of interest and reply with resume and salary requirements to:

Kathy Czupich, M.B.A., Director of Finance
E-mail:kathy@hepb.org
Institute for Hepatitis and Viral Research/
Pennsylvania Biotechnology Center
3805 Old Easton Road, Doylestown, PA 18902
Fax: 215-489-4920

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES
College of Pharmacy

The Department of Pharmaceutical Sciences invites applications for a tenure-track faculty position. Rank and salary are negotiable. The successful candidate will be expected to have an earned doctorate in pharmaceutical sciences or related discipline and to have a proven record of peer-reviewed research with ongoing federally funded grant support in an area complementary to College and/or campus research. Responsibilities include maintaining a funded research program and participating in graduate and professional education. Numerous opportunities exist for collaborations within the campus.

Application review will begin December 15, 2005. Interested candidates should forward a letter of interest, curriculum vitae, and contact information for at least three references to: **Russell B. Melchert, Ph.D., University of Arkansas for Medical Sciences College of Pharmacy, Department of Pharmaceutical Sciences, 4301 W. Markham, #522-3, Little Rock, AR 72205. Telephone: 501-686-6495; fax 501-686-6057; e-mail: melchertrussellb@uams.edu.** *The University of Arkansas for Medical Sciences is an Equal Opportunity/ Affirmative Action Employer.*

HEAD, DEPARTMENT of HUMAN NUTRITION, FOODS, and EXERCISE
Virginia Tech

Virginia Tech seeks a visionary Head for its Department of Human Nutrition, Foods, and Exercise (HNFE) **(website: http://www.hnfe.vt.edu)** in the College of Agriculture and Life Sciences **(website: http://www.cals.vt.edu).** The successful applicant will be expected to lead the HNFE Department in its mission of promoting human health through the integration of teaching, research and extension programs in nutrition, foods, and exercise. HNFE is one of the largest Departments within Virginia Tech's College of Agriculture and Life Sciences, with 21 faculty, 14 staff, approximately 900 undergraduate students, and 45 graduate students. For more information contact **Dr. Saied Mostaghimi** at **e-mail: smostagh@vt.edu** or **telephone: 540-231-6615.**

Applicants should apply online at **website: http://www.jobs.vt.edu** (job posting number 061062).

DIRECTOR, DIVISION OF GRADUATE EDUCATION
National Science Foundation, Arlington, Virginia

NSF's Directorate for Education and Human Resources seeks candidates for the position of Director, Division of Graduate Education (DGE). The Division leads the National Science Foundation's efforts to attract the most talented U.S. students into graduate studies, and to support them in their quest to become the leading scientists and engineers of the future. Information about the Division's activities may be found at **website: http://www.nsf.gov/ehr/dge/about.jsp.**

Appointment to this Senior Executive Service position may be on a career basis, on a one to three-year limited term basis, or by assignment under the Intergovernmental Personnel Act (IPA) provisions.

Announcement S20070005, with position requirements and application procedures are posted on NSF's home page at **website: http://www.nsf.gov/about/career_opps/.**

Applicants may also obtain the announcements by contacting **Executive Personnel Staff** at **telephone: 703-292-8755** *(hearing-impaired individuals may call TDD 703-292-8044).* Applications must be received by November 29, 2006.

NSF is an Equal Opportunity Employer.

ASSISTANT PROFESSOR

An accomplished scientist using biochemical, cellular, immunological, and/or genetic approaches to investigate infectious disease, zoonoses, or host response to infectious agents is sought for a Tenure-Track position (90 percent research, 10 percent instruction) in the Department of Veterinary Molecular Biology (VMB) at Montana State University. We are seeking an individual to complement or expand existing VMB expertise in the study of viral, protozoan, fungal, prion, and bacterial pathogens, as well as host responses against these pathogens. This position is funded by a competitive institutional salary (nine months), technician support, and a generous startup package. VMB is housed in a new research building (occupied in 2003) with state-of-the-art facilities for flow cytometry, cell biology, molecular sciences, and pathogen containment (BSL-3) facilities (completion date: spring 2007). A doctoral degree in a biomolecular discipline and postdoctoral experience are required. The potential to establish or evidence of a competitive, independent research program is required. Interested applicants should send a letter of application, curriculum vitae, selected reprints, a summary statement concerning research plans and grant proposals, and arrange for three letters of reference to be sent to: **Chair, Search Committee, Veterinary Molecular Biology, Montana State University, P.O. Box 173610, Bozeman, MT 59717-3610.** Screening will begin November 27, 2006, and will continue until a suitable applicant is hired. For a full job description and additional information about our Department visit our **website: http://vmb.montana.edu.** *ADA/Equal Opportunity/Affirmative Action/Veterans Preference.*

FACULTY POSITION
Experimental Biophysics

Tenure-track **ASSISTANT PROFESSOR,** position AA-0032-67, in Physics Department at Boise State University, starting fall 2007. Must participate in graduate programs, teach undergraduate and graduate courses, and develop externally funded research program. Review of applications begins 15 December 2006. Position description and application procedures are at **website: http://www.boisestate.edu/physics/biophysics.** *Boise State University is an Equal Opportunity Employer/Affirmative Action Employer. Veterans preferences.*

STANFORD UNIVERSITY DEPARTMENT OF CHEMICAL AND SYSTEMS BIOLOGY

The Department of Chemical and Systems Biology (formerly the Department of Molecular Pharmacology) at Stanford University School of Medicine invites applications for a tenure-track or tenured position at the **ASSISTANT or ASSOCIATE PROFESSOR** level. Candidates whose research interests lie at the interface of biomedical and physical sciences (e.g., chemical biology, quantitative biology, or systems biology) are particularly encouraged to apply. Stanford offers an outstanding environment for creative interdisciplinary biomedical research. Rank and salary are dependent on the candidate's qualifications. The predominant criterion for appointment in the University Tenure Line is a major commitment to research and teaching.

Candidates should have a Ph.D. and/or M.D. degree and postdoctoral research experience. Selection will begin immediately. Candidates should send curriculum vitae, a description of future research plans and the names of three references to:

James E. Ferrell, Jr., M.D. Ph.D.
c/o Jean Kavanagh, FAA
Department of Chemical
and Systems Biology
269 Campus Drive, CCSR Bldg
Room 3145A
Stanford University School of Medicine
Stanford CA 94305-5174

Stanford University is an Equal Opportunity, Affirmative Action Employer.

FACULTY POSITION UCI DEPARTMENT OF CHEMISTRY AND PROGRAM IN PHARMACEUTICAL SCIENCES

The Department of Chemistry and the Program in Pharmaceutical Sciences at the University of California, Irvine, jointly seek applicants for a tenure track position at the level of Assistant Professor, holding joint appointments in the Department of Chemistry and the Program in Pharmaceutical Sciences, beginning July 1, 2007. Applicants should have a PhD degree or equivalent with a strong record of research achievement in any area of chemistry related to pharmaceutical sciences and medicinal chemistry. We are particularly interested in applicants in the areas of synthetic biopolymers, structure-based drug discovery, drug delivery using biomaterials and/or nanotechnology, and biophysical chemistry related to drug action. Excellent oral and written communication skills are essential, as are superior teaching potential and relevant, high-impact publications in peer-reviewed journals. The successful candidate is expected to play a leading role in establishing a new UCI graduate program in pharmaceutical sciences, in collaboration with the UCI Pharmaceutical Sciences graduate program director and other faculty in Chemistry and Pharmaceutical Sciences; he or she will also participate in supporting an undergraduate major in this field. Primary teaching duties will be in medicinal chemistry and related courses at both the graduate and undergraduate levels. Accordingly, candidates must have a strong interest in interfacing medicinal chemistry with structural biology and pharmacology while developing an internationally recognized research program in chemistry.

To apply electronically, applicants should submit a letter of application, curriculum vitae, a set of research proposals, and at least 3 letters of recommendation. Application instructions can be found at **http://ps.uci.edu/employment/apply.html**. Review of applications will begin **November 15, 2006**. Position will remain open until filled. Information about programs can be found at **http://www.chem.uci.edu** or you may contact:

Professor Richard Chamberlin
Chair, Search Committee – Chemistry / Pharmaceutical Sciences
Department of Chemistry
University of California, Irvine
Irvine, CA 92697
Email: archambe@uci.edu

The University of California, Irvine is an Equal Opportunity/Affirmative Action Employer committed to excellence through diversity. UC Irvine has an active Career Partners Program and has an ADVANCE Gender Equity Program.

FLORIDA STATE UNIVERSITY

DEPARTMENT OF BIOLOGICAL SCIENCE TENURE-TRACK FACULTY POSITION IN ORGANISMAL BIOLOGY

The Department of Biological Science invites applications for a tenure-track faculty position in Organismal Biology. We welcome applications from any sub-discipline within Organismal Biology, but are particularly interested in the areas of behavior, physiological ecology, and biomechanics. Applicants should complement existing departmental strengths in ecology, evolutionary biology, marine biology, and paleobiology (**http://www.bio.fsu.edu/ee/index.html**).

We are seeking a candidate with notable research achievements, the ability to develop a well-funded independent research program, and a commitment to excellence in undergraduate and graduate education. We anticipate filling the position at the assistant professor level. Applicants should have a Ph.D. and postdoctoral experience.

This search will augment FSU's effort to enlarge the Biology Department through the construction of a new Life Science Research and Teaching Building and ongoing cluster hires of eight new faculty to Integrate the Genotype and Phenotype plus five new hires at our Marine and Coastal Laboratory. For detailed information please visit **www.bio.fsu.edu**.

To apply, please submit electronic copies (PDF files preferred) of a cover letter, curriculum vitae, statements of research plans and teaching interests, and the names and addresses of three references to: **Scott Steppan, Chair, Organismal Biology Search Committee, e-mail: facsearchorganismal@bio.fsu.edu**. Applications should be received by **December 4, 2006** for full consideration.

FSU is an Equal Opportunity Employer. Applications from minority and female candidates are especially encouraged.

FACULTY POSITIONS in MOLECULAR MICROBIOLOGY and EUKARYOTIC CELL BIOLOGY

The Department of Biology, in cooperation with the Center for Microbial Sciences and the SDSU Heart Institute, seeks to fill faculty positions at the assistant professor level with individuals having research interests in the areas of molecular microbiology or cell biology. Successful applicants will be expected to develop and maintain a vigorous, externally funded research program that complements the department's current strong emphasis in the microbial sciences and cardiovascular biology, participate in our undergraduate and graduate (M.S. and Ph.D.) teaching programs, and have the ability to interact with and mentor a diverse student body. Candidates with research interests in the following areas are desired: (a) molecular microbiologist interested in microbe-host interactions, physiology, genetics, immune evasion, evolution, and development of vaccines and/or therapeutics; or (b) an eukaryotic cell biologist focusing on use of cell biology and physiology methods for the study of basic cellular processes, including, but not limited to cardiovascular biology, developmental biology, neurobiology or stem cell biology.

The department is adjacent to the newly constructed BioScience Center and is housed in modern, newly renovated facilities that include a BSL3 lab, transgenic mouse core and flow cytometry facility. Applicants should submit a curriculum vitae, separate statements of research and teaching interests, three representative publications, and arrange for three letters of recommendation to be sent to either the **Cell Biology or the Microbiology Search Committee, Department of Biology, San Diego State University, San Diego, CA 92182-4614**. Review of applications will begin on **December 1, 2006** and will continue until the positions are filled. For more information see **http://www.bio.sdsu.edu/jobs**.

SDSU is a Title IX, Equal Opportunity Employer and does not discriminate against individuals on the basis of race, religion, national origin, sexual orientation, gender, marital status, age, disability or veteran status, including veterans of the Vietnam era.

POSITIONS OPEN

HEAD, OFFICE OF EXPERIMENTAL PROGRAM TO STIMULATE COMPETITIVE RESEARCH
National Science Foundation, Arlington, Virginia

NSF's Directorate for Education and Human Resources seeks candidates for the position of Head, Office of Experimental Program to Stimulate Competitive Research (EPSCoR). The Office assists the National Science Foundation in its statutory function to strengthen research and education in science and engineering throughout the United States and to avoid undue concentration of such research and education. Information about the Division's activities may be found at **website: http://www.nsf.gov/ehr/epscor/about.jsp.**

Appointment to this Senior Executive Service position may be on a career basis, on a one to three-year limited term basis, or by assignment under the Intergovernmental Personnel Act (IPA) provisions.

Announcement S20070007, with position requirements and application procedures are posted on NSF's home page at **website: http://www.nsf.gov/about/career_opps/.**

Applicants may also obtain the announcements by contacting **Executive Personnel Staff** at **telephone: 703-292-8755** (*hearing-impaired individuals may call TDD 703-292-8044).* Applications must be received by November 29, 2006.

NSF is an Equal Opportunity Employer.

The Department of Chemistry at the University of Dayton invites applications for a tenure-track faculty position in biochemistry at the rank of **ASSISTANT PROFESSOR** starting fall 2007. We seek individuals who will thrive in an environment that combines excellence in both teaching and research. The successful candidate will be expected to teach at all levels of the curriculum and establish an innovative, externally funded research program for both undergraduates and M.S. students. A Ph.D. in biochemistry or closely related field and at least one year of postdoctoral research experience are required. To apply, submit curriculum vitae, undergraduate/graduate transcripts, descriptions of teaching philosophy and research plans including equipment and startup needs and arrange to have three letters of recommendation sent to: **Search Committee, Department of Chemistry, University of Dayton, Dayton OH 45469-2357.** Review of applications will begin on November 23, 2006, and continue until the position is filled. For more information about the Department and the position, please visit **website: http://www.udayton.edu/~chem/biochemistry.** *The University of Dayton, a comprehensive Catholic University founded by the Society of Mary in 1850, is an Equal Opportunity/Affirmative Action Employer. Women, minorities, individuals with disabilities, and veterans are strongly encouraged to apply. The University of Dayton is firmly committed to the principle of diversity.*

The Department of Ecology and Evolutionary Biology, Tulane University, invites applications for two tenure-track positions, one in wetlands ecology and one in global change biology. One will be filled at the **ASSISTANT PROFESSOR** level and one at the **ASSOCIATE** or **FULL PROFESSOR** level. We invite applications at all levels for each position. See **website: http://www.tulane.edu/~ebio/News/positions.htm** for more details. Send curriculum vitae, statements of research and teaching interests, selected publications, and names and addresses of three references to: **Wetlands Ecologist Search** or **Global Change Biologist Search, Department of Ecology and Evolutionary Biology, 310 Dinwiddie Hall, Tulane University, New Orleans, LA 70118-5698.** Review of applications will begin December 1, 2006, and the searches will remain open until the positions are filled. These positions are subject to a final University determination on funding. *Tulane University is an Affirmative Action/Equal Employment Opportunity Employer.*

POSITIONS OPEN

HARVARD UNIVERSIY
Division of Engineering and Applied Sciences

The Division of Engineering and Applied Sciences at Harvard University invites applications for a faculty position in environmental applied mathematics, with particular application to engineering problems in the environment having chemical, physical, or biological aspects. The successful candidate will be expected to teach courses to support the curricula in both environmental engineering and applied mathematics. We intend to make this appointment at the **ASSISTANT** or, in exceptional cases, at the **ASSOCIATE PROFESSOR** level (untenured).

An application, assembled as a single PDF file, should include curriculum vitae, separate two-page statements of research and teaching interests, and up to three scientific papers. Three to five letters of recommendation should be requested and sent separately. Applications will be reviewed beginning December 31, 2006, although applications received after that date may also be considered.

Applications should be sent via **e-mail: environmental_appliedmathematics@deas.harvard.edu.** Letters of recommendation are also preferred by e-mail at the same address but may optionally be mailed to: **Chair, Environmental Applied Mathematics Search Committee, Division of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138.**

We particularly encourage applications from women and minorities. Harvard University is an Affirmative Action/Equal Opportunity Employer.

INVERTEBRATE CONSERVATION BIOLOGIST

The Department of Environmental Science and Policy (ESP) of George Mason University invites applications for a full-time, tenure-track **ASSISTANT PROFESSOR** position in invertebrate biology for August 2007. We seek an individual with a professional focus that complements current ESP faculty working in conservation biology and aquatic ecology. Experience with field-based or conservation genetic research is a plus. The successful candidate will be expected to pursue a vigorous externally funded research program, aspire to teaching excellence, collaborate with current faculty, and participate in our interdisciplinary graduate programs. Teaching duties will include undergraduate courses in animal biology, invertebrate biology, and a graduate course in the applicant's area of expertise. A Ph.D. is required.

George Mason University is a large, public University in Northern Virginia. ESP collaborates in B.S. and B.A. degrees in biology, and offers M.S. and Ph.D. degrees in environmental science and policy. Our faculty includes Ecologists, Biologists, Geologists, Oceanographers, and Policy Specialists. We have a strong history of research in both aquatic ecology and conservation biology and are planning a new satellite campus and field center at Belmont Bay on the tidal Potomac River adjacent to the Occoquan Bay National Wildlife Refuge (30 minutes from Fairfax) with diverse habitats ranging from open water and wetlands to upland meadows. For additional information see **websites: http://mason.gmu.edu/~espp** (Department) and **http://www.gmu.edu.**

Candidates should submit curriculum vitae, letter of intent including statements of research and teaching interests, examples of published work, teaching evaluations (if available), and contact information (with e-mail addresses) of three references to: **Dr. Andrea Weeks, I_Search Committee Chair, Department of Environmental Sciences and Policy, Mail Stop 5F2, George Mason University, Fairfax, VA 22030-4444.** Review of applications will begin on 11 December 2006. *George Mason University is an Affirmative Action/Equal Opportunity Employer. We strongly encourage women and minority candidates to apply.*

POSITIONS OPEN

LOUISIANA STATE UNIVERSITY SHREVEPORT (LSUS)
College of Sciences
Department of Biological Sciences

The Louisiana State University Shreveport (LSUS) Department of Biological Sciences invites applications for three anticipated **TENURE-TRACK POSITIONS** to begin in August 2007. LSUS is seeking innovative applicants with an active research program to engage students in experiential learning through basic and/or applied research, teaching, and service. Successful candidates will have earned a Ph.D. and have research emphasis in plant bioinformatics, computational biology, animal physiology, ecology, or other interdisciplinary life sciences.

For a complete position description and application procedures visit **website: http://www.lsus.edu/jobs.** To guarantee consideration, application materials must be received by December 8, 2006.

LSUS, a member of the Louisiana State University System, is an Affirmative Action/Equal Opportunity Employer.

ASSISTANT PROFESSOR
Biology

Buffalo State College, tenure-track Assistant Professor, Biology Department, to begin September 1, 2007. Competitive salary. Buffalo State College offers greenhouse facilities, a teaching herbarium, and access to a variety of field facilities.

Responsibilities: Teach evolution and plant biology courses at undergraduate and graduate level. Develop plant biology research program involving undergraduate and Master's-level students. Teach courses in intellectual foundations curriculum. Service to Department and College.

Required qualifications: Doctoral degree in biological sciences. Broad training and research experience in plant biology with strong background in evolutionary biology.

Preferred qualifications: Postdoctoral research and/or teaching experience. Research involving evolution, ecology, or physiology of plants.

Review of applications will begin December 1, 2006, and continue until position is filled. Send letter of application, curriculum vitae, statement of teaching and research interests, and contact information for three professional references to: **Search Committee Chair, Biology Department, Buffalo State College, SC 314, 1300 Elmwood Avenue, Buffalo, NY 14222-1095.** For more information about the College, visit **website: http://www.buffalostate.edu.** *Buffalo State is an Affirmative Action/Equal Opportunity Employer.*

FACULTY POSITION
DNA Forensic Biochemistry

Department of Chemistry and Molecular Biology, North Dakota State University (NDSU), has a tenure-track faculty position in DNA forensic biochemistry available fall 2007. Ph.D. in biochemistry or chemistry required. Postdoctoral experience and research related to the interests of the National Institute of Justice preferred. Teaching duties may include introductory biochemistry courses at the undergraduate or graduate levels and a graduate course related to DNA forensics. Must have potential to develop an externally funded, competitive research program, and commitment to teaching, and service. The position is open at the rank of **ASSISTANT or ASSOCIATE PROFESSOR.** Screening will begin December 1, 2006. For further information and application requirements see **website: http://www.ndsu.edu/ndsu/jobs/non_broadbanded/positions/00025232.shtml.**

Contact person: **Dr. S. Derek Killilea, Department of Chemistry and Molecular Biology North Dakota State University, Fargo, ND 58105. Telephone: 701-231-7946, fax: 701-231-8324.**

NDSU is an Equal Opportunity Institution.

Faculty Positions for 2007
Department of
Biochemistry and Molecular Genetics

University of Alabama at Birmingham
Schools of Medicine and Dentistry

Tenure track junior faculty positions and tenured senior faculty positions are available for investigators focused on modern areas of biochemistry and molecular genetics. Rank and tenure status commensurate with qualifications and experience. Areas of special emphasis include, but are not limited to, functional genomics, proteomics, adult and embryonic stem cell reprogramming, chromosome remodeling, and gene regulation in humans and in model organisms. Biochemists and structural biologists interested in protein-protein or protein-nucleic acid interactions are encouraged to apply. Nationally competitive salaries, start-up packages and space allocations will be offered to successful candidates. UAB is a highly interactive environment with strong basic and clinical sciences. Birmingham is a beautiful and affordable city with many cultural attractions.

Applicants should send a C.V., a summary of research interests and the names of three references before **January15, 2007** to:

Dr. Tim M. Townes, Chairman
Department of Biochemistry and Molecular Genetics
University of Alabama at Birmingham
Kaul Genetics Building, Room 502
720 20th Street South
Birmingham, Al 35294-0024
Email: ttownes@uab.edu

UAB is an Equal Opportunity/Affirmative Action Employer.

DEPARTMENT OF PATHOLOGY AND LABORATORY MEDICINE
DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA

Molecular Profiling of Immune System Pathology

The Department of Pathology and Laboratory Medicine at the David Geffen School of Medicine at UCLA is searching for outstanding scientists who are applying genomic, metagenomic, or proteomic approaches and computational innovation to study normal immunity and/or abnormalities within or mediated by the immune system. We are particularly interested in candidates whose work will provide mechanistic insights into the initiation and progression of immune pathologies and identify disease-associated molecular profiles (ie. 'Biomarkers'). Appointments may be at the tenure track Assistant Professor or tenured Associate/Full Professor level.

UCLA offers a highly collaborative research environment that promotes interactions between faculty in the School of Medicine, College of Letters and Science, the Jonsson Comprehensive Cancer Center, the California NanoSystems Institute, and the Crump Institute for Molecular Imaging. UCLA has also recently committed significant resources for the establishment of the Institute for Stem Cell Biology and Medicine (ISCBM), and faculty applying stem cell approaches to the above areas are particularly encouraged to apply. Candidates for tenured Associate/Full Professor positions must have well established and funded research programs. Assistant Professor applicants should have demonstrated their potential for research leadership. In all cases, emphasis will be placed on the applicant's record of research accomplishment, creativity, and promise of continuing success.

Candidates with a Ph.D. and/or M.D. degree should forward 2 hard copies of (1) a description of their research background; (2) full curriculum vitae; and (3) a list of 3-5 references. Electronic submissions will not be considered. Submit materials to: **Dr. Kenneth Dorshkind, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Los Angeles, CA 90095-1732.**

UC is an Affirmative Action/Equal Opportunity Employer. All qualified candidates, including women and minorities, are encouraged to apply.

Featured Employers

Search **ScienceCareers.org** for job postings from these employers. Listings updated three times a week.

Abbott Laboratories www.abbott.com

Elan Pharmaceuticals www.elan.com/careers

Genentech www.gene.com

Institute for One World Health
www.oneworldhealth.org

Invitrogen www.invitrogen.com/careers

Kelly Scientific Resources
www.kellyscientific.com

Novartis Institutes for BioMedical Research
www.nibr.novartis.com

Pfizer Inc.
www.pfizer.com

Pierce Biotechnology, Inc.
www.piercenet.com

If you would like to be a featured employer, call 202-326-6543.

ScienceCareers.org
We know science AAAS

Assistant Professor: Evolutionary Theory
University of California, Santa Barbara

The Department of Ecology, Evolution, and Marine Biology at the University of California, Santa Barbara seeks an interactive scientist who develops theory to address fundamental questions in evolutionary biology. Theorists whose research program additionally includes organismal, empirical or comparative approaches are also encouraged to apply. The appointment will be at the Assistant Professor level. The primary selection criteria for this position are excellence in both research and teaching. Applicants will be expected to teach courses at the undergraduate and graduate levels in evolutionary theory and in other areas according to their expertise. More details on the position can be found at **http://www.lifesci.ucsb.edu/eemb/department/jobs/jobs.html/**.

Applicants should submit an application letter together with a curriculum vitae, a statement of research accomplishments and future plans, a statement of teaching experience and interests, up to five selected reprints, and arrange for three letters of reference to be sent to:

Evolution Search Committee
Department of Ecology, Evolution, and Marine Biology
University of California
Santa Barbara, CA 93106-9610 U.S.A.

Alternatively, applications can be sent electronically to:
evolutionsearch@lifesci.ucsb.edu

Review of applicants will begin **January 3, 2007**, and will continue until the position has been filled.

The department is especially interested in candidates who can contribute to the diversity and excellence of the academic community through research, teaching and service.

UCSB is an Equal Opportunity Affirmative Action Employer.

POSITIONS OPEN

IRWIN BELK ENDOWED PROFESSORSHIP IN CANCER RESEARCH

The University of North Carolina at Charlotte (UNC Charlotte) is seeking applications for the Irwin Belk Endowed Professorship in Cancer Research to begin January 2008. The primary appointment for this **TENURED FULL PROFESSOR** position will be in the Department of Biology. Secondary appointments can be made in appropriate academic units in the College of Arts and Sciences, Engineering, and Computing and Informatics. All areas of cancer research will be considered; however, preference will be given to applicants whose research fosters collaborations with existing investigators studying liver pathophysiology, hematopoietic malignancies, tumor therapeutics, biomarker development/bioinformatics, biomedical engineering, and/or immunology. Successful applicants are expected to have a doctoral degree (e.g. Ph.D., M.D., D.D.S., D.V.M.) with qualifications commensurate with appointment as a Full Professor, including evidence of sustained scholarship and extramural research funding and demonstrated success collaborating with a diverse population of scientists. For additional information, see our **website: http://www.bioweb.uncc.edu.** Applicants should submit an electronic version (PDF or MSWord) of their curriculum vitae to **e-mail: klbost@e-mail.uncc.edu** or a copy by mail to: **Chair, Endowed Cancer Professor Search Committee, Department of Biology, University of North Carolina at Charlotte, 9201 University City Boulevard, Charlotte, NC 28223-0001.** Review of applications will begin December 6, 2006, and continue until the position is filled. *UNC Charlotte strives to create an academic climate in which the dignity of all individuals is respected and maintained. Therefore, we celebrate diversity that includes, but is not limited to ability/disability, age, culture, ethnicity, gender, language, race, religion, sexual orientation, and socio-economic status. Affirmative Action/Equal Opportunity Employer.*

ASSISTANT/ASSOCIATE PROFESSOR
Department of Pharmacology
The University of Toledo

The Department of Pharmacology, College of Pharmacy, at the University of Toledo is inviting applications for a tenure-track position available at the Assistant/Associate Professor level. Requirements include the Ph.D. in pharmacology, pharmaceutical sciences, or a related field and productive postdoctoral experience. Candidates with experience in the area of experimental therapeutics are encouraged to apply. Responsibilities for the position will include teaching undergraduate and graduate level courses in pharmacology or related areas. Current areas of research considered to be priorities for the health sciences initiative include: neurodegenerative diseases, cancer, organ transplantation/immunology, cardiovascular/diabetes and orthopedics. The successful candidate will be expected to develop and maintain an active, externally funded research program that complements existing research strengths within the Department and/or College. A competitive salary and research startup package will be provided.

Interested individuals are encouraged to submit curriculum vitae, a letter describing teaching philosophies and research goals, and arrange for three letters of reference to be sent to: **Miles Hacker, Ph.D., Chair of the Search Committee (PCN 996765), Department of Pharmacology, #607, The University of Toledo, College of Pharmacy, 2801 W. Bancroft Street, Toledo, OH 43606 (e-mail: miles.hacker@utoledo.edu).** Applicant review process will begin on November 15, 2006, and will continue until the position is filled.

The University of Toledo is an Equal Access, Equal Opportunity, Affirmative Action Employer and Educator. Women and minorities are encouraged to apply.

THE AMERICAN UNIVERSITY OF BEIRUT
Faculty Positions in Biology and Chemistry

The Faculty of Arts and Sciences at the American University of Beirut invites applications for academic positions in the Department of Biology, in the fields of microbiology and plant molecular biology; and in the Department of Chemistry in the fields of experimental physical chemistry and inorganic chemistry.

All positions are normally at the **ASSISTANT PROFESSOR** level to begin September 15, 2007, but appointments at **HIGHER RANKS and/or VISITING APPOINTMENTS** may also be considered. Appointments are for an initial period of three years. All advertised positions require a Ph.D. by the time of appointment. The usual teaching load is not more than nine hours a week. Sabbatical visitors are welcome. The language of instruction is English. For more information please visit **website: http://www.aub.edu.lb/~webfas/.**

Interested applicants should send a letter of application and curriculum vitae, and arrange for three letters of reference to be sent to: **Dean, Faculty of Arts and Sciences, American University of Beirut, c/o New York Office, 3 Dag Hammarskjold Plaza, 8th Floor, New York, NY 10017-2303 U.S.A.** or **Dean, Faculty of Arts and Sciences, American University of Beirut, P.O. Box 11-0236, Riad El-Solh, Beirut 1107 2020, Lebanon.** Electronic submissions may be sent to **e-mail: as_dean@aub.edu.lb.** All application materials should be received by December 29, 2006.

The American University of Beirut is an Affirmative Action, Equal Opportunity Employer.

TENURE-TRACK FACULTY POSITION
The Department of Structural and Cellular Biology
Tulane School of Medicine
Tulane University Health Sciences Center
New Orleans, Louisiana

The Department of Structural and Cellular Biology is seeking applications of all qualified candidates for a position (at the **ASSOCIATE PROFESSOR to PROFESSOR** level) as the **DIRECTOR OF ANATOMICAL TEACHING.** This individual would direct the gross and developmental anatomy course and assist in teaching medical histology. Candidates must have an earned doctorate (Ph.D. or M.D.). Prior experience in teaching of gross anatomy and medical histology is absolutely essential. Extramural research funding is not required, however, candidates with extramurally funded research programs in either cancer biology or neuroscience are of particular interest. The Department and Cancer Center are both undergoing major expansion and excellent startup, facilities, and environment will be provided. Applicants should submit a cover letter, curriculum vitae, summary of teaching experiences and philosophies, if applicable, a summary of research interests and plans and funding history, and letters of references to: **Dr. Steven M. Hill, Department of Structural and Cellular Biology, SL49, Tulane University Health Sciences Center, School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112** by December 15, 2006. *Tulane University is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.*

MOLECULAR GENETICIST. Tenure-track **ASSISTANT PROFESSOR** in the Biology Department at State University of New York (SUNY) Fredonia. Candidates must have a Ph.D. and postdoctoral experience. Teaching duties are genetics, plus majors and general education courses. A research program that promotes scholarship and involves students is expected. The complete list of application materials is listed on the Department website. Review of completed applications starts on November 8, 2006. Send materials to: **Genetics Search Committee, Department of Biology, State University of New York Fredonia, Fredonia, NY 14063.** See **website: http://www.fredonia.edu/humanresources/faculty.htm** for full ad. *An Affirmative Action/Equal Opportunity Employer, SUNY Fredonia encourages and actively seeks applications from minorities, women, and people with disabilities.*

The College of St. Scholastica
Learning to Touch the World

BIOLOGY. The Biology Department of the College of St. Scholastica invites applications for a tenure-track faculty appointment, beginning fall semester 2007, at the level of **ASSISTANT PROFESSOR.** The position is for teaching coursework in genetics, DNA analysis, general biology, and other courses as the need arises. Must have evidence of ability to work effectively with students and a strong commitment to undergraduate teaching. Student involvement in research is highly desirable. Ph.D. is required. Apply online at **website: http://www.csshrjobs.com.** Review of applications will begin immediately and will continue until the position is filled. The College of St. Scholastica is an independent comprehensive College in the Catholic Benedictine tradition with programs in the liberal arts and sciences and in professional career fields. Located on the scenic north shore of Lake Superior, Duluth is the educational/business/cultural/medical center of a region that includes the Midwest's most beautiful vacation areas. *All applicants must be authorized to work in the United States at the time of an offer of employment. Affirmative Action/Equal Opportunity Employer.*

PHYSICAL SCIENTIST
JILA, University of Colorado and National Institute of Standards and Technology (NIST), Boulder, Colorado

JILA, a premier academic research institute administered jointly by National Institute of Standards and Technology (NIST) and the University of Colorado, is searching for an outstanding Theoretical or Experimental Scientist to fill a Principal Investigator-level position at JILA.

Successful applicants would be expected to establish an internationally recognized research program involving graduate, undergraduate, and postdoctoral students, and to participate in departmental teaching responsibilities. We have particular interest in candidates applying advanced techniques to topics related to JILA's strengths in atomic, molecular, and optical science, laser technology, and precision measurement. Target areas include, but are not limited to, quantum information, quantum optics, quantum control, high-field physics, chemical physics, nanoscience, biophotonics, and instrumental astrophysics. JILA has a number of exceptionally successful faculty from underrepresented groups, and especially seeks applications from women and minority researchers. More information about JILA can be found at **website: http://jilawww.colorado.edu.**

Interested persons should send curriculum vitae which includes research and teaching experience, and a research proposal (one to two pages), as well as arrange for three letters of recommendation to be sent to: **JILA Search Committee, JILA, 440 UCB, University of Colorado, Boulder, CO 80309-0440.**

Application review will begin December 1, 2006.

For further information, contact **John Bohn** at **e-mail: bohn@murphy.colorado.edu, 303-492-5426,** or **Pam Leland** at **leland@jila.colorado.edu, telephone 303-492-4763.** *The University of Colorado at Boulder and NIST are both committed to diversity and equality in education and employment.*

CAREER OPPORTUNITY

This unique program offers the candidate with an earned doctorate in the life sciences the opportunity to obtain the Doctor of Optometry (OD) degree in 27 months (beginning in March of each year). Employment opportunities exist in research, education, industry, and private practice. Contact the **Admissions Office, telephone: 800-824-5526** at **The New England College of Optometry, 424 Beacon Street, Boston, MA 02115.** Additional information at **website: http://www.neco.edu, e-mail: admissions@neco.edu.**

CONFERENCE

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WELLCOME TRUST SCIENTIFIC CONFERENCE

ANIMAL HEALTH RESEARCH: RECENT DEVELOPMENTS AND FUTURE DIRECTIONS

24–26 January 2007

Wellcome Trust Conference Centre, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK

Background

The health of livestock is critically related to human health in developing countries and is a neglected research field. This meeting, hosted by the Wellcome Trust and sponsored by *Science* magazine, will review the current challenges in this area and will include issues around the translation of research into policy and practice.

As well as plenary sessions, the meeting will include workshops and poster sessions. For conference registration details visit:

www.wellcome.ac.uk/conferences

Please note there are a limited number of places for this meeting, priority will be given to scientists from developing countries.

Speakers include:

Professor Lonnie King, CDC/CCIID/NCID
Professor Don McManus, Queensland Institute of Medical Research
Professor Guy Palmer, Washington State University of Medical Research
Dr Jim Kaufman, Institute of Animal Health
Professor Louise Nel, University of Pretoria
Dr Mark Rweyemamu, Avis College
Professor Mark Woolhouse, University of Edinburgh
Professor Matthew Baylis, University of Liverpool
Professor Tom Barrett, Institute of Animal Health
Dr Jakob Zinsstag, Swiss Tropical Institute

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AWARDS

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MERCK

UNDERGRADUATE SCIENCE RESEARCH SCHOLARSHIP AWARDS

- 15 Awards Annually
- Scholarships up to $25,000
- Two Summer Internships at a Merck Research Facility

An applicant must:

- Be a full-time student at any four-year college or university
- Have junior year academic status
- Major in a life or physical science (first professional degrees excluded)
- Have a minimum cumulative GPA of 3.3 (4.0 point scale)

GRADUATE SCIENCE RESEARCH DISSERTATION FELLOWSHIPS

- 12 Fellowships Annually
- Fellowship Stipends up to $42,000
- Department Grants of $10,000
- Support for 12-24 months

An applicant must:

- Be enrolled full-time in a Ph.D. or equivalent doctoral program in a biomedical life or physical science
- Be engaged in and within 1-3 years of completing dissertation research

POSTDOCTORAL SCIENCE RESEARCH FELLOWSHIPS

- 10 Fellowships Annually
- Fellowship Stipends up to $70,000
- Department Grants of $15,000
- Support for 12-24 months

An applicant must:

- Hold a Ph.D. or equivalent degree in a biomedical life or physical science
- Be appointed as a new or continuing postdoctoral fellow by the end of 2007 at an academic or non-academic research institution (private industrial laboratories are excluded)

Applicants must be African American (Black), U.S. citizens or permanent residents, and attending an institution in the U.S.A. Applications must be submitted online at www.uncf.org/merck/ or postmarked by December 15, 2006

For more information, please contact your department chairperson or Jerry L. Bryant, Ph.D., at the **United Negro College Fund**, Inc., 8260 Willow Oaks Corporate Drive, P.O. Box 10444, Fairfax, VA 22031-4511, by fax (703) 205-3574, by e-mail at ***uncfmerck@uncf.org***.

The Program Proudly Announces the 2006 Canon Scholars

Denny Capps
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Burnaby, British Columbia, Canada

Wade T. Cooper
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Miami, Florida, U.S.A.

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Universidad de Buenos Aires
Buenos Aires, Argentina

Carl J. Legleiter
University of California, Santa Barbara
Santa Barbara, California, U.S.A.

Emily V. Saarinen
University of Florida
Gainesville, Florida, U.S.A.

Adrián Di Giacomo
Universidad de Buenos Aires
Buenos Aires, Argentina

Shannon Tushingham
University of California, Davis
Davis, California, U.S.A.

Carmen Wong
University of British Columbia
Vancouver, British Columbia, Canada

The Canon National Parks Science Scholars Program

Training the Next Generation of Conservation Scientists

About the Program

The Canon National Parks Science Scholars Program is a collaboration among Canon, the American Association for the Advancement of Science and the US National Park Service. The Program works to help create the next generation of environmental scientists.

For information about the Canon National Parks Science Scholars Program and a copy of the 2007 application guide, please visit the website at **www.canonscholars.org.**

Enter the 2007 Competition

Thanks to a generous commitment by Canon, the Program will award eight US$80,000 scholarships to PhD students throughout the Americas to conduct research critical to conserving the national parks of the region.

Research projects in the biological, physical, social and cultural sciences are eligible, as well as research projects in technology innovation in support of conservation sciences.

Applications are due 3 May 2007.

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NATIONAL PARK SERVICE

POSITIONS OPEN

ASSISTANT PROFESSOR, INTEGRATIVE/ COMPARATIVE ANIMAL BIOLOGIST

The Department of Biology and Marine Biology at the University of North Carolina Wilmington invites applications for a tenure-track position starting August 2007. The successful candidate will contribute to undergraduate and graduate courses in either cell/ molecular biology, biochemistry, immunology, physiology, virology, or a related course, maintain a vigorous, extramurally funded research program, and mentor graduate students. The Department offers B.S., M.S. and Ph.D. degrees. Excellent support for research is provided in departmental facilities on campus **(website: http://www.uncw.edu/bio/)** and at the Center for Marine Science **(website: http://www.uncw.edu/cmsr/).** Candidates must have a Ph.D. and postdoctoral experience. To apply, complete the online application available at **website: http://consensus.uncw.edu** by electronically submitting separately (1) a letter of application including brief statements of teaching and research interests, (2) curriculum vitae, and (3) contact information for three references. M.S. Word or Adobe PDF attachments are preferred. For questions about the position, contact: **Dr. Stephen Kinsey, Integrative/Comparative Animal Biologist Search Chair, e-mail: kinseys@uncw.edu, telephone: 910-962-7398.** For questions about the online application process, contact **Tracie Chadwick** at **e-mail: chadwickt@uncw.edu, telephone: 910-962-3536.** Application review will begin January 3, 2007. *Under North Carolina law, applications and related materials are confidential personnel documents and not subject to public release. UNCW conducts criminal background checks on finalists prior to offers of employment.*

UNC Wilmington is committed to Equal Employment Opportunity and is an Affirmative Action Employer. Minorities and women are encouraged to apply.

The NCI-designated Cancer Research Center of the Burnham Institute for Medical Research seeks outstanding **INDEPENDENT INVESTIGATORS** at all levels of faculty. Areas of special interest are: cancer stem cells, tumor microenvironment, ubiquitin-mediated signaling, chromatin remodeling and epigenetics, proteomics, chemical genomics, and chemical glycomics. The new faculty members will join a highly interactive and multidisciplinary research environment that includes the Cancer Center, San Diego Center for Chemical Genomics, Center on Proteolytic Pathways, an NIH-funded Human Stem Cell Center, state-of-the-art research core facilities, and impending support of stem cell research by the state of California. Candidates should e-mail their application, preferably in PDF format, to **e-mail: ccrecruit@burnham.org** by December 1, 2006. The application should include curriculum vitae, a description of past research, a description of proposed research, and copies of three representative publications. Candidates should arrange to have three letters of reference sent by e-mail to **e-mail: ccrecruit@burnham.org** or regular mail to: **Cancer Center Recruit Committee, c/o Kristiina Vuori, M.D., Ph.D., NCI Cancer Center, Burnham Institute for Medical Research, 10901 North Torrey Pines Road, La Jolla, CA 92037.** *Equal Opportunity Employer/Affirmative Action.*

FACULTY POSITIONS
The Scripps Research Institute (TSRI)
La Jolla, California

As part of a new research initiative at The Scripps Reseach Institute, we are seeking outstanding applicants for multiple tenure-track/tenured faculty positions at **ASSISTANT or ASSOCIATE PROFESSOR** levels. Applicants in all areas of chemistry and biology will be considered. Applicants should conduct innovative basic research that has the potential to contribute to translational medical research, and have demonstrated potential to be a leader in their field. Applicants should send their curriculum vitae, a brief statement of research interests, and three letters of reference to:

TSRI Faculty Search Committee
c/o Michelle Davis
The Scripps Research Institute
10550 N. Torrey Pines Road, STEIN202
La Jolla, CA 92037

POSITIONS OPEN

VA DESERT PACIFIC HEALTHCARE NETWORK

CAREER OPPORTUNITY

The Veterans Administration San Diego Healthcare System is currently seeking Physician applications for the **ASSOCIATE CHIEF OF STAFF** for research and development. The Associate Chief of Staff is responsible for the Medical Center's $55 million research program and its regulatory oversight. We offer excellent education, teaching, and clinical practice opportunities in a collaborative interdisciplinary setting. Comprehensive benefits package. *Must be U.S. citizen.* Direct questions to: **Jan Stock, Human Resources Specialist** at **telephone: 858-552-8585, ext. 7859.** *Equal Opportunity Employer.*

DIRECTOR, BIOTECHNOLOGY CORE. The Centers for Disease Control and Prevention is seeking a senior scientist to serve as the Director of the Biotechnology Core Facility **(website: http://www.biotech.cdc.gov/).** The Director will be the scientific and administrative leader to oversee Core laboratories within the facility, which include the DNA chemistry, protein chemistry, genome sequencing, microarray and suspension array activities and bioinformatics. The Director will be expected to seek internal and external funding for instrumentation and support for facility operations through user fees and coordination of new multi-investigator research funding initiatives. Additional responsibilities include coordination of user training and facility-sponsored workshops. The Director can expect to develop collaborative relationships with researchers including Microbiologists, Medical Epidemiologists, Bioinformaticians, and Information Technology Specialists. This position represents a unique opportunity to study molecular profiles of human pathogens in one of the nation's most recognized agencies.

A Ph.D. in chemistry, microbiology or related area with documented five plus years of expertise in genomics, proteomics, or protein mass spectrometry is required; experience directing biotechnology core activities is highly desirable. Inquiries made before December 1, 2006, can be directed to **Dr. Patricia Wilkins** at **e-mail: pma1@cdc.gov.** *CDC is an Equal Opportunity Employer.*

RESEARCH ASSOCIATE THREE OR FOUR (MICROSCOPY IMAGING SPECIALIST)
Department of Biological Sciences

The Socolofsky Microscopy Facility at Louisiana State University **(website: http://www.biology.lsu.edu/facilities/micro_fac/)** has state-of-the-art light microscopy equipment, including confocal and deconvolution imaging. Required qualifications for Research Associate Three: Bachelor's or equivalent degree in biological science or related field with three years of relevant experience or a Master's degree with one year of experience; experience in confocal light microscopy. Research Associate Four: Master's degree with two years of relevant experience or Ph.D.; experience in confocal light microscopy. Responsibilities: images acquisition and analysis, user training, and oversight of light microscopes and multi-user digital imaging equipment. *An offer of employment is contingent on a satisfactory pre-employment background check.* Application deadline is November 10, 2006, or until candidate is selected. Submit letter of application and resume (including e-mail address), and two letters of recommendation to: **Ms. Charyl Thompson, Department of Biological Sciences, 202 Life Sciences Building Louisiana State University, Reference #014225, Baton Rouge, LA 70803. E-mail: cthomps@lsu.edu.**

Louisiana State University is an Equal Opportunity/Equal Access Employer.

POSITIONS OPEN

TENURE-TRACK ASSISTANT PROFESSOR POSITIONS IN PLANT BIOLOGY AND ANIMAL DEVELOPMENT

The Department of Biology, University of Wisconsin-Stevens Point, offers two tenure-track, nine-month faculty positions in plant biology and animal development beginning August 2007. We seek candidates committed to undergraduate education in a Department focused on enhancing faculty, student, and curricular diversity.

Both positions require teaching introductory biology and upper-division courses; research involving undergraduates, student advising, and Department service. Ph.D. and experience commensurate with teaching in a quality undergraduate Department are required. Research and teaching specialty areas open. Postdoctoral research, publications, grants, and educational excellence are viewed favorably.

Plant biology: Ph.D. in one or more of the following plant biology disciplines: anatomy, development, horticulture, or paleobotany. .

Animal development: Ph.D. in animal development. Teaching includes general biology, principles of genetics, and developmental biology.

The Department encourages applications from individuals of underrepresented groups, those with experience teaching underrepresented individuals, and those that incorporate diversity content in their teaching.

Appointment at **ASSISTANT PROFESSOR.** Address application materials to: **Dr. Robert Bell, Chair; Biology Department, University of Wisconsin-Stevens Point; Stevens Point, WI 54481-3897,** and include curriculum vitae, statements of teaching philosophy and research interests, recommendation letters (three), and undergraduate and graduate transcripts. Review begins 28 November 2006, and will continue until filled. For more information, **telephone: 715-346-2074; fax: 715-346-3624; e-mail: rbell@uwsp.edu.**

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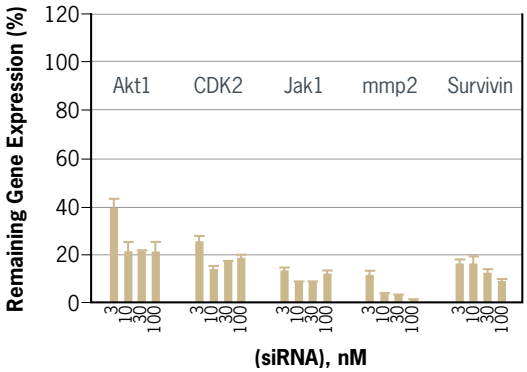

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